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(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: GROSS, Mitchell, S. [US/US]; 667 Pugh Road, Wayne, PA 19087 (US). SWEET, Raymond, W. [US/US]; 108 Edgehill Road, Bala Cynwyd, PA 19004 (US). TAYLOR, Geraldine [GB/GB]; Compton, Newbury, Berkshire RG20 7NN (GB).

(74) Agents: BAUMEISTER, Kirk et al.; Smithkline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406–0939 (US).

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(54) Title: HUMAN MONOCLONAL ANTIBODY

(57) Abstract

This invention relates to novel human monoclonal antibodies (mAbs) and to the genes encoding same. More specifically, this invention relates to human monoclonal antibodies specifically reactive with an epitope of the fusion (F) protein of Respiratory Syncytial Virus (RSV). Such antibodies are useful for the therapeutic and/or prophylactic treatment of RSV infection in human patients, particularly infants and young children.

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HUMAN MONOCLONAL ANTIBODY

Field of the Invention

This invention relates to novel human monoclonal antibodies (mAbs) and to the genes encoding same. More specifically, this invention relates to human monoclonal antibodies specifically reactive with an epitope of the fusion (F) protein of Respiratory Syncytial Virus (RSV). Such antibodies are useful for the therapeutic and/or prophylactic treatment of RSV infection in human patients, particularly infants and young children.

Background of the Invention

Respiratory syncytial virus (RSV) is the major cause of lower respiratory disease in children, giving rise to predictable annual epidemics of bronchiolitis and pneumonia in children worldwide. The virus is highly contagious, and infections can occur at any age. Comprehensive details concerning RSV infection and its clinical features can be obtained from excellent recent reviews by McIntosh, K. and R. M. Chanock, In: "Respiratory Syncytial Virus", Ch. 38, B.N. Fields ed., Raven Press (1990) and Hall, C.B., In: "Textbook of Pediatric Disease" Feigin and Cherry, eds., W.B. Saunders, pgs 1247-1268 (1987).

RSV is distributed worldwide. One of the most remarkable features of the epidemiology of RSV virus, as mentioned above, is the consistent pattern of infection and disease. Other respiratory viruses cause epidemics at irregular intervals or exhibit a mixed endemic/epidemic pattern, but RSV is the only respiratory viral pathogen that produces a sizable epidemic every year in large urban centers. In the

temperate areas of the world, RSV epidemics have occurred primarily in the late fall, winter or spring but never during the summer. The occurrence and spread of infection within a community is characteristic and easily diagnosed, leading to sharp rises in cases of bronchiolitis and pediatric pneumonia and the number of hospital admissions of young children with acute lower respiratory tract disease. Other respiratory viral agents that occur in outbreaks are rarely present at the same time as RSV.

Primary RSV infection occurs in the very young. Zero to 2 year old infants are the most susceptible and represent the primary affected population. In this group, 1 out of 5 will develop lower respiratory (below larynx) disease upon infection and this ratio stays the same upon reinfection. By 1 year of age, 25-50% of infants have specific antibodies as a result of natural infection and this is close to 100% by age 4-5. Thus, virtually all children have been infected before they have entered school.

Age, sex, socioeconomic and environmental factors can all influence the severity of disease. Hospitalization is required in 1-3% of cases of RSV infection and is usually of long duration (up to 3 weeks). The high morbidity of RSV infection, especially in infancy, has also been implicated in the development of respiratory problems later in life. With current intensive care in the U.S. and the other developed countries, overall mortality for normal subjects is low (less than 2% of hospitalized subjects). However, mortality is much higher in less developed countries and, even in developed countries, mortality is high in certain risk groups such as in infants with underlying cardiac condition (cyanotic congenital heart disease) or

respiratory disease (bronchopulmonary dysplasia) where the progression of symptoms may be rapid. For instance, mortality in infants with cyanotic congenital heart disease has been reported to be as high as 37%. In premature infants apneic spells due to RSV infection may occur and, in rare cases, cause neurologic or systemic damage. Severe lower respiratory tract illness (bronchiolitis and pneumonia) is most common in patients under six months of age. Infants who have apparently recovered completely from this illness may display symptomatic respiratory abnormalities for years (recurrent wheezing, decreased pulmonary function, recurrent cough, asthma, and bronchitis).

Immunity to RSV appears to be short-lived, thus reinfections are frequent. The mechanisms by which the immune system protects against RSV infection and reinfection are not well understood. It is clear, however, that immunity is only partially protective since reinfection is common at all ages, and sometimes occurs in infants only weeks after recovery from a primary infection. Both serum and secretory antibodies (IgA) have been detected in response to RSV infection in adults as well as in very young infants. However, the titers of serum antibodies to the viral F or G glycoprotein, as well as of neutralizing antibodies found in infants (1-8 months of age) are 15-25% of those found in older subjects. These reduced titers may contribute to the increased incidence of serious infection in younger children.

Evidence for the role of serum antibodies in protection against RSV virus has emerged from epidemiological as well as animal studies. In adults exposed naturally to the virus, susceptibility correlated well with low serum antibody level. In

infants, titers of maternally transmitted antibodies correlate with resistance to serious disease [Glezen, W.P. *et al.*, J. Pediatr. 98:708-715 (1981)]. Other studies show that the incidence and severity of lower respiratory tract involvement is diminished in the presence of high serum antibody [McIntosh, K. *et al.*, J. Infect. Dis. 138:24-32 (1978)] and high titers of passively administered serum neutralizing antibodies have been shown to be protective in a cotton rat model of RSV infection [Prince, G. A. *et al.*, Virus Res. 3:193-206 (1985)].

Children lacking cell-mediated immunity are unable to overcome their infection and shed virus for many months in contrast to children with normal immune systems. Similarly, nude mice infected with RSV virus persistently shed virus. These mice can be cured by adoptive transfer of primed T cells [Cannon, M. J. *et al.*, Immunology 62:133-138 (1987)].

In summary, it appears that both cellular and humoral immunity are involved in protection against infection, reinfection and RSV disease and that although antigenic variation is limited, protective immunity is not complete even after multiple exposures.

RSV, belonging to the family paramyoxoviridae, is a negative-strand unsegmented RNA virus with properties similar to those of the paramyxoviruses. It has, however been placed in a separate genus Pneumovirus, based on morphologic differences and lack of hemagglutinin and neuraminidase activities. RSV is pleomorphic and ranges in size from 150-300 nm in diameter. The virus matures by budding from the outer membrane of a cell and virions appear as membrane-bound particles with short, closely spaced projections or "spikes". The RNA genome encodes 10 unique viral

polypeptides ranging in size from 9.5 kDa to 160 kDa [Huang, Y. T. and G. W. Wertz, J. Virol. 43:150-157 (1982)]. Seven proteins (F, G, N, P, L, M, M2) are present in RSV virions and at least three proteins (F, G, and SH) are expressed on the surface of infected cells. The F protein [SEQ ID NO: 20] has been conclusively identified as the protein responsible for cell fusion since specific antibodies to this protein inhibit syncytia formation *in vitro* and cells infected with vaccinia virus expressing recombinant F protein form syncytia in the absence of other RSV virus proteins. In contrast, antibodies to the G protein do not block syncytia formation but prevent attachment of the virus to cells.

RSV can be divided into two antigenically distinct subgroups, (A & B) [Mufson, M. A. *et al.*, J. Gen'l. Virol. 66:2111-2124 (1985)]. This antigenic dimorphism is linked primarily to the surface attachment (G) glycoprotein [Johnson, R. A. *et al.*, Proc. Nat'l. Acad. Sci. USA 84:5625-5629 (1987)]. Strains of both group A and B circulate simultaneously, but the proportion of each may vary unpredictably from year to year. An effective therapy must therefore target both subgroups of the virus and this is the reason for the selection of the highly conserved surface fusion (F) protein as target antigen for mAb therapy as will be discussed later.

The induction of neutralizing antibodies to RSV virus appears to be limited to the F and G surface glycoproteins. Of these two proteins, the F protein is the major target for cross-reactive neutralizing antibodies associated with protection against different strains of RSV virus. In addition, experimental vaccination of mice or cotton rats with F protein also

results in cross protection. The antigenic relatedness of the F protein across strains and subgroups of the virus is reflected in its high degree of homology at the amino acid level. In contrast, in the two subgroups and various strains of RSV, antigenic dimorphism was linked primarily to the G glycoprotein. The F protein has a predicted molecular weight of 68-70 kDa; a signal peptide at its N-terminus; a membrane anchor domain at its C terminus; and is cleaved proteolytically in the infected cell prior to virion assembly to yield disulfide linked F_2 and F_1. Five neutralizing epitopes have been identified within the F protein sequence [SEQ ID NO: 20] and map to residues 205-225; 259-278; 289-299; 483-488 and 417-438. Studies to determine the frequency of sequence diversion in the F protein [SEQ ID NO: 20] showed that the majority of the neutralizing epitopes were conserved in all of the 23 strains of RSV virus isolated in Australia, Europe, and regions of the U.S. over a period of thirty years. In another study, seroresponses of forty three infants and young children to primary infection with subgroup A or a subgroup B strain showed that responses to homologous and heterologous F antigens were not significantly different, while the G proteins of the subgroup A and B strains were quite unrelated. Moreover, antibody inhibition of virus-mediated cell fusion *in vitro* versus inhibition of infection correlates best with protection in animal models and fusion inhibition is primarily restricted to F protein specific antibodies.

Prophylactic treatment for RSV infection is thus desirable for the high risk groups of children as well as for all children in underdeveloped countries. However, a vaccine for RSV infection is not currently available. Severe safety issues surrounding an

attenuated whole virus vaccine tested in the 1960s, as well as the potential of induced immunopathology associated with the newer candidate subunit vaccines make the prospects of a vaccine in the near future appear remote. To date one drug therapy, Ribavirin, a broad spectrum antiviral, has been approved. Ribavirin has gained only minimal acceptance owing to problems of administration, mild toxicity and questionable efficacy. In the majority of cases, hospitalized children receive no drug therapy and receive only intensive supportive care which is extremely costly. It is clear that there is a need for a safe, effective and easily administered drug for the treatment of RSV infection.

The use of passive antibody therapy in humans is well documented and is being used to treat other infectious diseases such as hepatitis and cytomegalovirus. The feasibility of passive antibody treatment/protection against RSV has been well established using animal models. Most of the earlier passive transfer studies in animals against infectious agents, including RSV, utilized murine mABs. Studies in animals have clearly demonstrated that polyclonal and monoclonal antibody against both F and G glycoprotein can confer passive protection in RSV virus infection when given prophylactically or therapeutically [Prince, *et al.*, supra]. In these studies, passive transfer of neutralizing F or G mAbs to mice, cotton rats or monkeys, significantly reduce or completely prevent replication of the RSV virus in the lungs. However, as discussed above, clearly, the F protein is the more important target for antibody therapy.

Recently, the FDA has approved for use intravenous gammaglobulins (IVIG) isolated from pooled human sera. Initial reports from this study had been encouraging

[Groothuis, J. R. *et al.*, Antimicrob. Agents Chemo. 35(7):1469-1473 (1991)]. However, generic shortcomings of IVIGs exist and include, without limitation, the fact that such products are human blood derived and grams of antibody often need to be administered to achieve an effective dose.

Alternatively, monoclonal antibodies have been employed. The advantages of such an approach include: a higher concentration of specific antibody can be achieved thereby reducing the amount of globulin required to be given; the reliance on direct blood products can be eliminated; the levels of antibody in the preparation can be more uniformly controlled and the routes of administration can be extended. While passive immunotherapy employing monoclonal antibodies from a heterologous species (e.g., murine) has been suggested (See: PCT Application PCT/US94/08699, Publication No. WO 95/04081), one alternative to reduce the risk of an undesirable immune response on the part of the patient directed against the foreign antibody is to employ "humanized" antibodies. These antibodies are substantially of human origin, with only the Complementarity Determining Regions (CDRs) being of non-human origin. Particularly useful examples of this approach are disclosed in PCT Application PCT/GB91/01554, Publication No. WO 92/04381 and PCT Application PCT/GB93/00725, Publication No. WO93/20210. Clinical trials are on-going to evaluate the efficacy of humanized antibodies for treatment of RSV infection in young children.

A second and more preferred approach is to employ fully human mAbs. Unfortunately, there have been few successes in producing human monoclonal antibodies through classic hybridoma technology. Indeed,

acceptable human fusion partners have not been identified and murine myeloma fusion partners do not work well with human cells, yielding unstable and low producing hybridoma lines. However, recent advances in molecular biology and immunology make it now possible to isolate human mABs, particularly directed against foreign infectious agents.

Fully human mAbs to RSV F protein [SEQ ID NO: 20] remain a desirable option for the treatment of this disease. Although some success has been reported in obtaining fragments of such mAbs [Barbas, C.F. *et al.*, Proc. Nat'l. Acad. Sci. USA 89:10164-10168 (1992); Crowe, J. E. *et al.*, Proc. Nat'l. Acad. Sci. USA 91: 1386-1390 (1994) and PCT application number PCT/US93/08786, published as WO94/06448, March 31, 1994)], the achievement of such results is not straightforward. Novel human mABs, when and however obtained, are particularly useful alone or in combination with existing molecules to form immunotherapeutic compositions.

There exists a need in the art for useful prophylactic compositions for the prevention or passive treatment of RSV.

Brief Description of the Invention

In one aspect, this invention provides fully human monoclonal antibodies and functional fragments thereof specifically reactive with an F protein epitope of RSV and capable of neutralizing RSV infection. These human mABs specific for the F protein of RSV virus may be useful to passively treat or prevent infection.

In another aspect, the present invention provides modifications to neutralizing single chain Fv fragments (scFV) specific for the F protein of RSV produced by

random combinatorial cloning of human antibody sequences and isolated from a filamentous phage Fab display library.

In still another aspect, there is provided a reshaped or altered human antibody containing human heavy and light chain constant regions from a first human donor and heavy and light chain variable regions or the CDRs thereof derived from human neutralizing monoclonal antibodies for the F protein of RSV derived from a second human donor.

In yet another aspect, the present invention provides a pharmaceutical composition which contains one (or more) altered or reshaped antibodies and a pharmaceutically acceptable carrier.

In yet another aspect, the invention provides a pharmaceutical composition comprising at least one dose of an immunotherapeutically effective amount of the reshaped, altered or monoclonal antibody of this invention in combination with at least one additional monoclonal, altered or reshaped antibody. A particular embodiment is provided in which the additional antibody is an anti-RSV antibody distinguished from the subject antibody of the invention by virtue of being reactive with a different epitope of the RSV F protein antigen than the subject antibody of the invention.

In a further aspect, the present invention provides a method for passive immunotherapy of RSV disease in a human by administering to said human an effective amount of the pharmaceutical composition of the invention for the prophylactic or therapeutic treatment of RSV infection.

In yet another aspect, the present invention provides methods for, and components useful in, the recombinant production of human and altered antibodies

(e.g., engineered antibodies, CDRs, Fab or $F(ab)_2$ fragments, or analogs thereof) which are derived from human neutralizing monoclonal antibodies (mAbs) for the F protein of RSV. These components include isolated nucleic acid sequences encoding same, recombinant plasmids containing the nucleic acid sequences under the control of selected regulatory sequences which are capable of directing the expression thereof in host cells (preferably mammalian) transfected with the recombinant plasmids. The production method involves culturing a transfected host cell line of the present invention under conditions such that the human or altered antibody is expressed in said cells and isolating the expressed product therefrom.

In still another aspect of the invention is a method to diagnose the presence of RSV in a human which comprises contacting a sample of biological fluid with the human antibodies and altered antibodies and fragments thereof of the instant invention and assaying for the occurrence of binding between said human antibody (or altered antibody, or fragment) and RSV.

Other aspects and advantages of the present invention are described further in the detailed description and the preferred embodiments thereof.

Brief Description of the Drawings

Fig. 1A is a graph illustrating the competition of Gλ-1 scFV phage binding with RSV19 mAb [International patent publication No. WO92/04381, published March 19, 1992].

Fig. 1B is a graph illustrating the competition of Gλ-1 scFV phage binding with RSV B4 mAb [International patent publication No. WO93/20210, published October 14, 1993].

Fig. 2 is a graph illustrating virus neutralization by scFV phages, Gλ-1, Gλ-3, and G_K-1 with RSV strain 273.

Fig. 3 illustrates the DNA sequence [SEQ ID NO: 1] and protein sequence (amino acids reported in single letter code) [SEQ ID NO: 2] for the Gλ-1 light chain variable region, processed N-terminus through framework IV.

Fig. 4 illustrates the DNA sequence [SEQ ID NO: 3] and protein sequence (amino acids reported in single letter code) [SEQ ID NO: 4] for the Gλ-1 heavy chain variable region, processed N-terminus through framework IV.

Fig. 5 illustrates the cloning strategy used for the construction of the Gλ-1 monoclonal antibody. The heavy chain V region was cloned into the pCD derivative vector as a *Xho*I - *Apa*I fragment. The entire light chain V region was cloned into the pCN derivative vector, 43-1pcn, as a *Sac*I - *Avr*II fragment. Details are described below.

Fig. 6 provides a comparison of the heavy chain amino acid sequences of the Gλ-1 single chain F_v [SEQ ID NO: 5] and various monoclonal antibodies of this invention. The amino acid sequences of the heavy chains for the A [SEQ ID NO: 7] and B [SEQ ID NO: 8] constructs are shown. Numbering of the residues is based on the germline (GL) gene Dp58 [SEQ ID NO: 6], beginning at the mature processed amino terminus and ending at CDR3. The "-" indicates identity to the preceding sequence (eg., A compared to B). Bold residues correspond to the leader region, and to CDRs 1-3.

Fig. 7 provides a comparison of the light chain amino acid sequences of the Gλ-1A single chain F_v [SEQ ID NO: 9] and various monoclonal antibodies of this

invention. The amino acid sequences of the light chains for the A [SEQ ID NO: 11] and B [SEQ ID NO: 12] constructs are shown. Numbering of the residues in the Vκ region is based on the germline (GL) gene DpL8 [SEQ ID NO: 10], beginning at the mature processed amino terminus and ending at CDR3. For reference to framework 4, the actual numbering is also shown for Gλ-1A. As in Fig. 6, the "-" indicates identity to the preceding sequence.

Figs. 8A to 8F illustrate the continuous DNA sequence [SEQ ID NO: 13] of the expression plasmid Gλ-1Apcd containing the RSV neutralizing human Gλ-1 mAb for the heavy chain. The start of translation, leader peptide, amino-terminal processing site, carboxy terminus of the Gλ-1 heavy chain, and *Eco* RI restriction endonuclease cleavage site are shown.

Figs. 9A to 9E illustrate the continuous DNA sequence [SEQ ID NO: 14] of the expression plasmid Gλ-1Apcn containing the RSV neutralizing human Gλ-1 mAb for the light chain. The corresponding features for the light chain as for Figs. 8A-8F are shown.

Figs. 10A and 10B illustrate the continuous DNA sequence [SEQ ID NO: 15] of the coding region of the heavy chain of plasmid Gλ-1Bpcd. Bolded residues indicate differences from the full vector sequence for Gλ-1Apcd in Figs. 8A-8F [SEQ ID NO: 13].

Fig. 11 is the DNA sequence [SEQ ID NO: 16] of the coding region for the light chain of plasmid Gλ-1Bpcn. Bolded residues indicate differences from the full vector sequence for Gλ-1Apcn in Figs. 9A-9E [SEQ ID NO: 14].

Detailed Description of the Invention

This invention provides useful human monoclonal antibodies (and fragments thereof) reactive with the F protein of RSV, isolated nucleic acids encoding same and various means for their recombinant production as well as therapeutic, prophylactic and diagnostic uses of such antibodies and fragments thereof.

I. Definitions.

As used in this specification and the claims, the following terms are defined as follows:

"Altered antibody" refers to a protein encoded by an altered immunoglobulin coding region, which may be obtained by expression in a selected host cell. Such altered antibodies are engineered antibodies (e.g., chimeric, humanized, or reshaped or immunologically edited human antibodies) or fragments thereof lacking all or part of an immunoglobulin constant region, e.g., Fv, Fab, or $F(ab')_2$ and the like.

"Altered immunoglobulin coding region" refers to a nucleic acid sequence encoding an altered antibody of the invention or a fragment thereof.

"Reshaped human antibody" refers to an altered antibody in which minimally at least one CDR from a first human monoclonal donor antibody is substituted for a CDR in a second human acceptor antibody. Preferrably all six CDRs are replaced. More preferrably an entire antigen combining region (e.g., Fv, Fab or $F(ab')_2$) from a first human donor monoclonal antibody is substituted for the corresponding region in a second human acceptor monoclonal antibody. Most preferrably the Fab region from a first human donor is operatively linked to the appropriate constant regions of a second human acceptor antibody to form a full length monoclonal antibody.

"First immunoglobulin partner" refers to a nucleic acid sequence encoding a human framework or human immunoglobulin variable region in which the native (or naturally-occurring) CDR-encoding regions are replaced by the CDR-encoding regions of a donor human antibody. The human variable region can be an immunoglobulin heavy chain, a light chain (or both chains), an analog or functional fragments thereof. Such CDR regions, located within the variable region of antibodies (immunoglobulins) can be determined by known methods in the art. For example, Kabat *et al.* (Sequences of Proteins of Immunological Interest, 4th Ed., U.S. Department of Health and Human Services, National Institutes of Health (1987)) disclose rules for locating CDRs. In addition, computer programs are known which are useful for identifying CDR regions/structures.

"Second fusion partner" refers to another nucleotide sequence encoding a protein or peptide to which the first immunoglobulin partner is fused in frame or by means of an optional conventional linker sequence (i.e., operatively linked). Preferably the fusion partner is an immunoglobulin gene and when so, it is referred to as a "second immunoglobulin partner". The second immunoglobulin partner may include a nucleic acid sequence encoding the entire constant region for the same (i.e., homologous - the first and second altered antibodies are derived from the same source) or an additional (i.e., heterologous) antibody of interest. It may be an immunoglobulin heavy chain or light chain (or both chains as part of a single polypeptide). The second immunoglobulin partner is not limited to a particular immunoglobulin class or isotype. In addition, the second immunoglobulin partner may comprise part of an immunoglobulin constant region, such as found

in a Fab, or $F(ab)_2$ (i.e., a discrete part of an appropriate human constant region or framework region). A second fusion partner may also comprise a sequence encoding an integral membrane protein exposed on the outer surface of a host cell, e.g., as part of a phage display library, or a sequence encoding a protein for analytical or diagnostic detection, e.g., horseradish peroxidase (HRP), β-galactosidase, etc.

The terms Fv, Fc, Fd, Fab, or $F(ab')_2$ are used with their standard meanings [see, e.g., Harlow *et al.*, Antibodies A Laboratory Manual, Cold Spring Harbor Laboratory, (1988)].

As used herein, an "engineered antibody" describes a type of altered antibody, i.e., a full-length synthetic antibody (e.g., a chimeric, humanized, reshaped or immunologically edited human antibody as opposed to an antibody fragment) in which a portion of the light and/or heavy chain variable domains of a selected acceptor antibody are replaced by analogous parts from one or more donor antibodies which have specificity for the selected epitope. For example, such molecules may include antibodies characterized by a humanized heavy chain associated with an unmodified light chain (or chimeric light chain), or vice versa. Engineered antibodies may also be characterized by alteration of the nucleic acid sequences encoding the acceptor antibody light and/or heavy variable domain framework regions in order to retain donor antibody binding specificity. These antibodies can comprise replacement of one or more CDRs (preferably all) from the acceptor antibody with CDRs from a donor antibody described herein.

A "chimeric antibody" refers to a type of engineered antibody which contains naturally-occurring

variable region (light chain and heavy chains) derived from a donor antibody in association with light and heavy chain constant regions derived from an acceptor antibody from a heterologous species.

A "humanized antibody" refers to a type of engineered antibody having its CDRs derived from a non-human donor immunoglobulin, the remaining immunoglobulin-derived parts of the molecule being derived from one (or more) human immunoglobulin(s). In addition, framework support residues may be altered to preserve binding affinity [see, e.g., Queen *et al.*, Proc. Nat'l. Acad. Sci. USA, 86:10029-10032 (1989), Hodgson *et al.*, Bio/Technology, 9:421 (1991)].

An "immunologically edited antibody" refers to a type of engineered antibody in which changes are made in donor and/or acceptor sequences to edit regions in respect of cloning artifacts, germ line enhancements, etc. aimed at reducing the likelihood of an immunological response to the antibody on the part of a patient being treated with the edited antibody.

The term "donor antibody" refers to an antibody (monoclonal, or recombinant) which contributes the nucleic acid sequences of its variable regions, CDRs, or other functional fragments or analogs thereof to a first immunoglobulin partner, so as to provide the altered immunoglobulin coding region and resulting expressed altered antibody with the antigenic specificity and neutralizing activity characteristic of the donor antibody. One donor antibody suitable for use in this invention is a Fab fragment of a human neutralizing monoclonal antibody designated as Fab Gλ-1. Fab Gλ-1 is defined as a having the variable light and heavy chain DNA and amino acid sequences Gλ-1 as shown in Figs. 3, 4, 8A-8F and 9A-9E [SEQ ID NOS: 1-4, 13 and 14].

The term "acceptor antibody" refers to an antibody (monoclonal or recombinant) from a source genetically unrelated to the donor antibody, which contributes all (or any portion, but preferably all) of the nucleic acid sequences encoding its heavy and/or light chain framework regions and/or its heavy and/or light chain constant regions to the first immunoglobulin partner. Preferably a human antibody is the acceptor antibody.

"CDRs" are defined as the complementarity determining region amino acid sequences of an antibody which are the hypervariable regions of immunoglobulin heavy and light chains [see, e.g., Kabat *et al.*, Sequences of Proteins of Immunological Interest, 4th Ed., U.S. Department of Health and Human Services, National Institutes of Health (1987)]. There are three heavy chain and three light chain CDRs (or CDR regions) in the variable portion of an immunoglobulin. Thus, "CDRs" as used herein refers to all three heavy chain CDRs, or all three light chain CDRs (or both all heavy and all light chain CDRs, if appropriate). CDRs provide the majority of contact residues for the binding of the antibody to the antigen or epitope. CDRs of interest in this invention are derived from donor antibody variable heavy and light chain sequences, and include analogs of the naturally occurring CDRs, which analogs also share or retain the same antigen binding specificity and/or neutralizing ability as the donor antibody from which they were derived.

By "sharing the antigen binding specificity or neutralizing ability" is meant, for example, that although Fab Gλ-1 may be characterized by a certain level of antigen affinity, a CDR encoded by a nucleic acid sequence of Fab Gλ-1 in an appropriate structural environment may have a lower, or higher affinity. It is

expected that CDRs of Fab Gλ-1 in such environments will nevertheless recognize the same epitope(s) as does the intact Fab Gλ-1. A "functional fragment" is a partial heavy or light chain variable sequence (e.g., minor deletions at the amino or carboxy terminus of the immunoglobulin variable region) which retains the same antigen binding specificity and/or neutralizing ability as the antibody from which the fragment was derived.

An "analog" is an amino acid sequence modified by at least one amino acid, wherein said modification can be a chemical modification, or a substitution or a rearrangement of a few amino acids (i.e., no more than 10), which modification permits the amino acid sequence to retain the biological characteristics, e.g., antigen specificity and high affinity, of the unmodified sequence. For example, (silent) mutations can be constructed, via substitutions, when certain endonuclease restriction sites are created within or surrounding CDR-encoding regions.

Analogs may also arise as allelic variations. An "allelic variation or modification" is an alteration in the nucleic acid sequence encoding the amino acid or peptide sequences of the invention. Such variations or modifications may be due to degeneracy in the genetic code or may be deliberately engineered to provide desired characteristics. These variations or modifications may or may not result in alterations in any encoded amino acid sequence.

The term "effector agents" refers to non-protein carrier molecules to which the altered antibodies, and/or natural or synthetic light or heavy chains of the donor antibody or other fragments of the donor antibody may be associated by conventional means. Such non-protein carriers can include conventional carriers used

in the diagnostic field, e.g., polystyrene or other plastic beads, polysaccharides, e.g., as used in the BIAcore (Pharmacia) system, or other non-protein substances useful in the medical field and safe for administration to humans and animals. Other effector agents may include a macrocycle, for chelating a heavy metal atom, or radioisotopes. Such effector agents may also be useful to increase the half-life of the altered antibodies, e.g., polyethylene glycol.

II. Combinatorial Cloning.

As mentioned above, a number of problems have hampered the direct application of the hybridoma technology [G. Kohler and C. Milstein, Nature, 256: 495-497 (1975)] to the generation and isolation of human monoclonal antibodies. Among these are a lack of suitable fusion partner myeloma cell lines used to form hybridoma cell lines as well as the poor stability of such hybridomas even when formed. These shortcomings are further exacerbated in the case of RSV because of the paucity of viral specific B cells in the peripheral circulation. Therefore, the molecular biological approach of combinatorial cloning is preferred.

Combinatorial cloning is disclosed generally in PCT Publication No. WO90/14430. Simply stated, the goal of combinatorial cloning is to transfer to a population of bacterial cells the immunological genetic capacity of a human cell, tissue or organ. It is preferred to employ cells, tissues or organs which are immunocompetent. Particularly useful sources include, without limitation, spleen, thymus, lymph nodes, bone marrow, tonsil and peripheral blood lymphocytes. The cells may be optionally RSV stimulated *in vitro*, or selected from donors which are known to have produced an immune response or donors who are HIV^+ but asymptomatic.

The genetic information isolated from the donor cells can be in the form of DNA or RNA and is conveniently amplified by Polymerase Chain Reaction (PCR) or similar techniques. When isolated as RNA the genetic information is preferably converted into cDNA by reverse transcription prior to amplification. The amplification can be generalized or more specifically tailored. For example, by a careful selection of PCR primer sequences, selective amplification of immunoglobulin genes or subsets within that class of genes can be achieved.

Once the component gene sequences are obtained, in this case the genes encoding the variable regions of the various heavy and light antibody chains, the light and heavy chain genes are associated in random combinations to form a random combinatorial library. Various recombinant DNA vector systems have been described to facilitate combinatorial cloning [see: PCT Publication No. WO90/14430 supra; Scott and Smith, Science 249:386-406 (1990); or U. S. Patent 5,223,409]. Having generated the combinatorial library, the products can, after expression, be conveniently screened by biopanning with RSV F protein or, if necessary, by epitope blocked biopanning as described in more detail below.

As described herein, it is preferred to use single chain antibodies for combinatorial cloning and screening and then to convert them to full length mAbs after selection of the desired candidate molecules. However, Fab fragments of mAbs can also be used for cloning and screening.

III. Antibody Fragments.

The present invention contemplates the use of scFv, Fab, or $F(ab')_2$ fragments to derived full-length mAbs directed against the F protein of RSV. Although these

fragments may be independently useful as protective and therapeutic agents *in vivo* against RSV-mediated conditions or *in vitro* as part of an RSV diagnostic, they are employed herein as a component of a reshaped human antibody. A scFv fragment contains the light and heavy chain variable regions joined by a linker of about 12 amino acids in either a light-linker-heavy or a heavy-linker-light orientation. A Fab fragment contains the entire light chain and amino terminal portion of the heavy chain; and a $F(ab')_2$ fragment is the fragment formed by two Fab fragments bound by additional disulfide bonds. RSV binding monoclonal antibodies provide sources of scFv or Fab fragments which can be obtained from a combinatorial phage library [see, e.g., Winter *et al.*, Ann. Rev. Immunol., 12:433-455 (1994) or Barbas *et al.*, Proc. Nat'l. Acad. Sci. (USA) 89, 10164-10168 (1992), which are both hereby incorporated by reference in their entireties].

IV. Anti-RSV Antibody Amino Acid and Nucleotide Sequences of Interest.

The Fab Gλ-1 or other antibodies described herein may contribute sequences, such as variable heavy and/or light chain peptide sequences, framework sequences, CDR sequences, functional fragments, and analogs thereof, and the nucleic acid sequences encoding them, useful in designing and obtaining various altered antibodies which are characterized by the antigen binding specificity of the donor antibody.

As one example, the present invention thus provides variable light chain and variable heavy chain sequences from the RSV human Fab Gλ-1A and sequences derived therefrom. The heavy chain variable region of Fab Gλ-1A is illustrated by Figs. 4, 8A-8F and 10A-10B [SEQ ID NOS: 3-4, 13 and 15].

The nucleic acid sequences of this invention, or fragments thereof, encoding the variable light chain and heavy chain peptide sequences are also useful for mutagenic introduction of specific changes within the nucleic acid sequences encoding the CDRs or framework regions, and for incorporation of the resulting modified or fusion nucleic acid sequence into a plasmid for expression. For example, silent substitutions in the nucleotide sequence of the framework and CDR-encoding regions can be used to create restriction enzyme sites which would facilitate insertion of mutagenized CDR (and/or framework) regions. These CDR-encoding regions may be used in the construction of reshaped human antibodies of this invention.

Taking into account the degeneracy of the genetic code, various coding sequences may be constructed which encode the variable heavy and light chain amino acid sequences, and CDR sequences of the invention as well as functional fragments and analogs thereof which share the antigen specificity of the donor antibody. The isolated nucleic acid sequences of this invention, or fragments thereof, encoding the variable chain peptide sequences or CDRs can be used to produce altered antibodies, e.g., chimeric or humanized antibodies, or other engineered antibodies of this invention when operatively combined with a second immunoglobulin partner.

It should be noted that in addition to isolated nucleic acid sequences encoding portions of the altered antibody and antibodies described herein, other such nucleic acid sequences are encompassed by the present invention, such as those complementary to the native CDR-encoding sequences or complementary to the human framework regions surrounding the CDR-encoding regions. Such sequences include all nucleic acid sequences which

by virtue of the redundancy of the genetic code are capable of encoding the same amino acid sequence as given in Figs. 3 and 4 [SEQ ID NOS: 2 and 4]. Figs. 6 and 7 [SEQ ID NOS: 5-12] provide representations of such sequences. Other useful DNA sequences encompassed by this invention include those sequences which hybridize under stringent hybridization conditions [See: T. Maniatis *et al.*, Molecular Cloning (A Laboratory Manual), Cold Spring Harbor Laboratory (1982), pages 387 to 389] to the DNA sequences encoding the Gλ-1 antibodies (e.g., sequences of Figs. 3, 4, 8A-8F through 11 [SEQ ID NOS: 1-4, 13-16]) and which retain the antigen binding properties of those antibodies. An example of one such stringent hybridization condition is hybridization at 4XSSC at 65°C, followed by a washing in 0.1XSSC at 65°C for an hour. Alternatively an exemplary stringent hybridization condition is in 50% formamide, 4XSSC at 42°C. Preferably, these hybridizing DNA sequences are at least about 18 nucleotides in length, i.e., about the size of a CDR.

V. Altered Immunoglobulin Coding Regions and Altered Antibodies.

Altered immunoglobulin coding regions encode altered antibodies which include engineered antibodies such as chimeric antibodies, humanized, reshaped, and immunologically edited human antibodies. A desired altered immunoglobulin coding region contains CDR-encoding regions in the form of scFv regions that encode peptides having the antigen specificity of an RSV antibody, preferably a high affinity antibody such as provided by the present invention, inserted into an acceptor immunoglobulin partner.

When the acceptor is an immunoglobulin partner, as defined above, it includes a sequence encoding a second

antibody region of interest, for example, an Fc region. Immunoglobulin partners may also include sequences encoding another immunoglobulin to which the light or heavy chain constant region is fused in frame or by means of a linker sequence. Engineered antibodies directed against functional fragments or analogs of RSV may be designed to elicit enhanced binding with the same antibody.

The immunoglobulin partner may also be associated with effector agents as defined above, including non-protein carrier molecules, to which the immunoglobulin partner may be operatively linked by conventional means.

Fusion or linkage between the immunoglobulin partners, e.g., antibody sequences, and the effector agent may be by any suitable means, e.g., by conventional covalent or ionic bonds, protein fusions, or hetero-bifunctional cross-linkers, e.g., carbodiimide, glutaraldehyde, and the like. Such techniques are known in the art and readily described in conventional chemistry and biochemistry texts.

Additionally, conventional linker sequences which simply provide for a desired amount of space between the second immunoglobulin partner and the effector agent may also be constructed into the altered immunoglobulin coding region. The design of such linkers is well known to those of skill in the art.

In addition, signal sequences for the molecules of the invention may be modified to enhance expression. For example the reshaped human antibody having the signal sequence and CDRs derived from the Fab Gλ-1 heavy chain sequence, may have the original signal peptide replaced with another signal sequence such as the Campath leader sequence [Page, M. J. *et al.*, BioTechnology 9:64-68(1991)].

An exemplary altered antibody, a reshaped human antibody, contains a variable heavy and the entire light chain peptide or protein sequence having the antigen specificity of Fab Gλ-1, fused to the constant heavy regions C_{H-1}-C_{H-3} derived from a second human antibody.

In still a further embodiment, the engineered antibody of the invention may have attached to it an additional agent. For example, the procedure of recombinant DNA technology may be used to produce an engineered antibody of the invention in which the Fc fragment or $C_{H-2}C_{H-3}$ domain of a complete antibody molecule has been replaced by an enzyme or other detectable molecule (i.e., a polypeptide effector or reporter molecule).

Another desirable protein of this invention may comprise a complete antibody molecule, having full length heavy and light chains, or any discrete fragment thereof, such as the Fab or $F(ab')_2$ fragments, a heavy chain dimer, or any minimal recombinant fragments thereof such as an F_V or a single-chain antibody (SCA) or any other molecule with the same specificity as the selected donor Fab Gλ-1. Such protein may be used in the form of an altered antibody, or may be used in its unfused form.

Whenever the immunoglobulin partner is derived from an antibody different from the donor antibody, e.g., any isotype or class of immunoglobulin framework or constant regions, an engineered antibody results. Engineered antibodies can comprise immunoglobulin (Ig) constant regions and variable framework regions from one source, e.g., the acceptor antibody, and one or more (preferably all) CDRs from the donor antibody, e.g., the anti-RSV antibody described herein. In addition, alterations, e.g., deletions, substitutions, or additions, of the

acceptor mAb light and/or heavy variable domain framework region at the nucleic acid or amino acid levels, or the donor CDR regions may be made in order to retain donor antibody antigen binding specificity or to reduce potential immunogenicity.

Such engineered antibodies are designed to employ one (or both) of the variable heavy and/or light chains of the RSV mAb (optionally modified as described) or one or more of the below-identified heavy or light chain CDRs. The engineered antibodies of the invention are neutralizing, i.e., they desirably inhibit virus growth *in vitro* and *in vivo* in animal models of RSV infection.

Such engineered antibodies may include a reshaped human antibody containing the human heavy and light chain constant regions fused to the RSV antibody functional fragments. A suitable human (or other animal) acceptor antibody may be one selected from a conventional database, e.g., the KABAT® database, Los Alamos database, and Swiss Protein database, by homology to the nucleotide and amino acid sequences of the donor antibody. A human antibody characterized by a homology to the framework regions of the donor antibody (on an amino acid basis) may be suitable to provide a heavy chain constant region and/or a heavy chain variable framework region for insertion of the donor CDRs. A suitable acceptor antibody capable of donating light chain constant or variable framework regions may be selected in a similar manner. It should be noted that the acceptor antibody heavy and light chains are not required to originate from the same acceptor antibody.

Desirably the heterologous framework and constant regions are selected from human immunoglobulin classes and isotypes, such as IgG (subtypes 1 through 4), IgM, IgA and IgE. The Fc domains are not limited to native

sequences, but include mutant variants known in the art that alter function. For example, mutations have been described in the Fc domains of certain IgG antibodies that reduce Fc-mediated complement and Fc receptor binding [see, e.g., A. R. Duncan *et al.*, Nature, 332:563-564 (1988); A. R. Duncan and G. Winter, Nature, 332:738-740 (1988); M.-L. Alegre *et al.*, J. Immunol., 148:3461-3468 (1992); M.-H. Tao *et al.*, J. Exp. Med., 178:661-667 (1993); and V. Xu *et al.* J. Biol. Chem., 269:3469-2374 (1994)]; alter clearance rate [J.-K. Kim *et al.*, Eur. J. Immunol., 24:542-548 (1994)]; and reduce structural heterogeneity [S. Angal *et al.*, Mol. Immunol. 30:105-108 (1993)]. Also, other modifications are possible such as oligomerization of the antibody by addition of the tailpiece segment of IgM and other mutations [R. I. F. Smith and S. L. Morrison, Biotechnology 12:683-688 (1994); R. I. F. Smith *et al.*, J. Immunol., 154: 2226-2236 (1995)] or addition of the tailpiece segment of IgA [I. Kariv *et al.*, J. Immunol., 157: 29-38 (1996)]. However, the acceptor antibody need not comprise only human immunoglobulin protein sequences. For instance a gene may be constructed in which a DNA sequence encoding part of a human immunoglobulin chain is fused to a DNA sequence encoding a non-immunoglobulin amino acid sequence such as a polypeptide effector or reporter molecule.

The altered antibody thus preferably has the structure of a natural human antibody or a fragment thereof, and possesses the combination of properties required for effective therapeutic use, e.g., treatment of RSV mediated diseases in man, or for diagnostic uses.

It will be understood by those skilled in the art that an altered antibody may be further modified by changes in variable domain amino acids without

necessarily affecting the specificity and high affinity of the donor antibody (i.e., an analog). It is anticipated that heavy and light chain amino acids may be substituted by other amino acids either in the variable domain frameworks or CDRs or both. Particularly preferred is the immunological editing of such reconstructed sequences as illustrated in the examples herein.

In addition, the variable or constant region may be altered to enhance or decrease selective properties of the molecules of the instant invention, as described above. For example, dimerization, binding to Fc receptors, or the ability to bind and activate complement [see, e.g., Angal *et al.*, Mol. Immunol, 30:105-108 (1993); Xu *et al.*, J. Biol. Chem, 269:3469-3474 (1994); and Winter *et al.*, EP 307,434-B].

Such antibodies are useful in the prevention and treatment of RSV mediated disorders, as discussed below.

VI. Production of Altered antibodies and Engineered Antibodies.

The resulting reshaped human antibodies of this invention can be expressed in recombinant host cells, e.g., COS, CHO or myeloma cells. A conventional expression vector or recombinant plasmid is produced by placing these coding sequences for the altered antibody in operative association with conventional regulatory control sequences capable of controlling the replication and expression in, and/or secretion from, a host cell. Regulatory sequences include promoter sequences, e.g., CMV promoter, and signal sequences, which can be derived from other known antibodies. Similarly, a second expression vector can be produced having a DNA sequence which encodes a complementary antibody light or heavy chain. Preferably this second expression vector is

identical to the first except insofar as the coding sequences and selectable markers are concerned. This ensures as far as possible that each polypeptide chain is functionally expressed. Alternatively, the heavy and light chain coding sequences for the altered antibody may reside on a single vector.

A selected host cell is co-transfected by conventional techniques with both the first and second vectors (or simply transfected by a single vector) to create the transfected host cell of the invention comprising both the recombinant or synthetic light and heavy chains. The transfected cell is then cultured by conventional techniques to produce the engineered antibody of the invention. The production of the antibody which includes the association of both the recombinant heavy chain and light chain is measured in the culture by an appropriate assay, such as an enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay (RIA). Similar conventional techniques may be employed to construct other altered antibodies and molecules of this invention.

Suitable vectors for the cloning and subcloning steps employed in the methods and construction of the compositions of this invention may be selected by one of skill in the art. For example, the conventional pUC series of cloning vectors, may be used. One vector used is pUC19, which is commercially available from supply houses, such as Amersham (Buckinghamshire, United Kingdom) or Pharmacia (Uppsala, Sweden). Any vector, which is capable of replicating readily, has an abundance of cloning sites and selectable genes (e.g., antibiotic resistance), and is easily manipulated, may be used for cloning. Thus, the selection of the cloning vector is not a limiting factor in this invention.

Similarly, the vectors employed for expression of the engineered antibodies according to this invention may be selected by one of skill in the art from any conventional vectors. Preferred vectors include for example plasmids pCD or pCN. The vectors also contain selected regulatory sequences (such as CMV promoters) which direct the replication and expression of heterologous DNA sequences in selected host cells. These vectors contain the above described DNA sequences which code for the engineered antibody or altered immunoglobulin coding region. In addition, the vectors may incorporate the selected immunoglobulin sequences modified by the insertion of desirable restriction sites for ready manipulation.

The expression vectors may also be characterized by genes suitable for amplifying expression of the heterologous DNA sequences, e.g., the mammalian dihydrofolate reductase gene (DHFR). Other preferable vector sequences include a polyadenylation (polyA) signal sequence, such as from bovine growth hormone (BGH) and the betaglobin promoter sequence (betaglopro). The expression vectors useful herein may be synthesized by techniques well known to those skilled in this art.

The components of such vectors, e.g. replicons, selection genes, enhancers, promoters, signal sequences and the like, may be obtained from commercial or natural sources or synthesized by known procedures for use in directing the expression and/or secretion of the product of the recombinant DNA in a selected host. Other appropriate expression vectors of which numerous types are known in the art for mammalian, bacterial, insect, yeast, and fungal expression may also be selected for this purpose.

The present invention also encompasses a cell line transfected with a recombinant plasmid containing the coding sequences of the engineered antibodies or altered immunoglobulin molecules thereof. Host cells useful for the cloning and other manipulations of these cloning vectors are also conventional. However, most desirably, cells from various strains of *E. coli* are used for replication of the cloning vectors and other steps in the construction of altered antibodies of this invention.

Suitable host cells or cell lines for the expression of the engineered antibody or altered antibody of the invention are preferably mammalian cells such as CHO, COS, a fibroblast cell (e.g., 3T3), and myeloid cells, and more preferably a CHO or a myeloid cell. Human cells may be used, thus enabling the molecule to be modified with human glycosylation patterns. Alternatively, other eukaryotic cell lines may be employed. The selection of suitable mammalian host cells and methods for transformation, culture, amplification, screening and product production and purification are known in the art. See, e.g., Sambrook *et al.*, Molecular Cloning (A Laboratory Manual), 2nd edit., Cold Spring Harbor Laboratory (1989).

Bacterial cells may prove useful as host cells suitable for the expression of the recombinant scFvs, Fabs and MAbs of the present invention [see, e.g., Plückthun, A., Immunol. Rev., 130:151-188 (1992)]. The tendency of proteins expressed in bacterial cells to be in an unfolded or improperly folded form or in a non-glycosylated form does not pose as great a concern because Fabs are not normally glycosylated and can be engineered for exported expression, thereby reducing the high concentration that facilitates misfolding.

Nevertheless, any recombinant Fab produced in a bacterial cell would be screened for retention of antigen binding ability. If the molecule expressed by the bacterial cell was produced and exported in a properly folded form, that bacterial cell would be a desirable host. For example, various strains of *E. coli* used for expression are well-known as host cells in the field of biotechnology. Various strains of *B. subtilis*, *Streptomyces*, other bacilli and the like may also be employed in this method.

Where desired, strains of yeast cells known to those skilled in the art are also available as host cells, as well as insect cells, e.g. *Drosophila* and *Lepidoptera* and viral expression systems [see, e.g. Miller *et al.*, Genetic Engineering, 8:277-298, Plenum Press (1986) and references cited therein].

The general methods by which the vectors of the invention may be constructed, the transfection methods required to produce the host cells of the invention, and culture methods necessary to produce the altered antibody of the invention from such host cell are all conventional techniques. Likewise, once produced, the altered antibodies of the invention may be purified from the cell culture contents according to standard procedures of the art, including ammonium sulfate precipitation, affinity columns, column chromatography, gel electrophoresis and the like. Such techniques are within the skill of the art and do not limit this invention.

Yet another method of expression of reshaped antibodies may utilize expression in a transgenic animal. An exemplary systems is described in U. S. Patent No. 4,873,316. The expression system described in that reference uses the animal's casein promoter and,

when transgenically incorporated into a mammal, permits the female to produce the desired recombinant protein in its milk.

Once expressed by the desired method, the engineered antibody is then examined for *in vitro* activity by use of an appropriate assay. At present, conventional ELISA assay formats are employed to assess qualitative and quantitative binding of the altered antibody to RSV. Additionally, other *in vitro* assays and *in vivo* animal models may also be used to verify neutralizing efficacy prior to subsequent human clinical studies performed to evaluate the persistence of the altered antibody in the body despite the usual clearance mechanisms.

VII. Therapeutic/Prophylactic Uses.

This invention also relates to a method of treating humans experiencing RSV-related symptoms which comprises administering an effective dose of antibodies including one or more of the antibodies (altered, reshaped, monoclonal, etc.) described herein or fragments thereof.

The therapeutic response induced by the use of the molecules of this invention is produced by binding to RSV and thus subsequently blocking RSV propagation. Thus, the molecules of the present invention, when in preparations and formulations appropriate for therapeutic use, are highly desirable for those persons experiencing RSV infection. For example, longer treatments may be desirable when treating seasonal episodes or the like. The dose and duration of treatment relates to the relative duration of the molecules of the present invention in the human circulation, and can be adjusted by one of skill in the art depending upon the condition being treated and the general health of the patient.

The altered antibodies, antibodies and fragments thereof of this invention may also be used alone or in conjunction with other antibodies, particularly human or humanized mAbs reactive with other epitopes on the F protein or other RSV target antigens as prophylactic agents.

The mode of administration of the therapeutic and prophylactic agents of the invention may be any suitable route which delivers the agent to the host. The altered antibodies, antibodies, engineered antibodies, and fragments thereof, and pharmaceutical compositions of the invention are particularly useful for parenteral administration, i.e., subcutaneously, intramuscularly, intravenously, or intranasally.

Therapeutic and prophylactic agents of the invention may be prepared as pharmaceutical compositions containing an effective amount of the altered antibody of the invention as an active ingredient in a pharmaceutically acceptable carrier. An aqueous suspension or solution containing the antibody, preferably buffered at physiological pH, in a form ready for injection is preferred. The compositions for parenteral administration will commonly comprise a solution of the engineered antibody of the invention or a cocktail thereof dissolved in an pharmaceutically acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers may be employed, e.g., 0.4% saline, 0.3% glycine, and the like. These solutions are sterile and generally free of particulate matter. These solutions may be sterilized by conventional, well known sterilization techniques (e.g., filtration). The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and

buffering agents, etc. The concentration of the antibody of the invention in such pharmaceutical formulation can vary widely, i.e., from less than about 0.5%, usually at or at least about 1% to as much as 15 or 20% by weight and will be selected primarily based on fluid volumes, viscosities, etc., according to the particular mode of administration selected.

Thus, a pharmaceutical composition of the invention for intramuscular injection could be prepared to contain 1 mL sterile buffered water, and between about 1 ng to about 100 mg, e.g. about 50 ng to about 80 mg, or more preferably, about 5 mg to about 75 mg, of an engineered antibody of the invention. Similarly, a pharmaceutical composition of the invention for intravenous infusion could be made up to contain about 250 ml of sterile Ringer's solution, and about 1 to about 75 and preferably 5 to about 50 mg/ml of an engineered antibody of the invention. Actual methods for preparing parenterally administrable compositions are well known or will be apparent to those skilled in the art and are described in more detail in, for example, Remington's Pharmaceutical Science, 15th ed., Mack Publishing Company, Easton, Pennsylvania.

It is preferred that the therapeutic and prophylactic agents of the invention, when in a pharmaceutical preparation, be present in unit dose forms. The appropriate therapeutically effective dose can be determined readily by those of skill in the art. To effectively treat an inflammatory disorder in a human or other animal, one dose of approximately 0.1 mg to approximately 20 mg per 70 kg body weight of a protein or an antibody of this invention should be administered parenterally, preferably i.v. or i.m. (intramuscularly).

Such dose may, if necessary, be repeated at appropriate time intervals selected as appropriate by a physician.

The altered antibodies and engineered antibodies of this invention may also be used in diagnostic regimens, such as for the determination of RSV mediated disorders or tracking progress of treatment of such disorders. As diagnostic reagents, these altered antibodies may be conventionally labeled for use in ELISAs and other conventional assay formats for the measurement of RSV levels in serum, plasma or other appropriate tissue, or the release by human cells in culture. The nature of the assay in which the altered antibodies are used are conventional and do not limit this disclosure.

The antibodies, altered antibodies or fragments thereof described herein can be lyophilized for storage and reconstituted in a suitable carrier prior to use. This technique has been shown to be effective with conventional immunoglobulins and art-known lyophilization and reconstitution techniques can be employed.

The following examples illustrate various aspects of this invention including the construction of exemplary engineered antibodies and expression thereof in suitable vectors and host cells, and are not to be construed as limiting the scope of this invention. All amino acids are identified by conventional three letter or single letter codes. All necessary restriction enzymes, plasmids, and other reagents and materials were obtained from commercial sources unless otherwise indicated. All general cloning ligation and other recombinant DNA methodology were as performed in T. Maniatis *et al.*, cited above, or Sambrook *et al.*, cited above.

Example 1: Isolation of Gλ-1 scFv-1

Single chain (sc) Fv libraries were prepared from an individual purposely exposed to RSV and selected against recombinant RSV F-protein following described procedures [R. H. Jackson *et al*, in *Protein Engineering, A Practical Approach*, A. R. Rees *et al* eds, Oxford University Press, chapter 12, pp. 277-301, 1992; H. R. Hoogenboom *et al.*, Nucl. Acid Res., 19: 4133-4137 (1991); J. D. Marks *et al.*, J. Mol. Biol., 222: 581-597 (1991)]. Briefly, lymphocytes were isolated from a blood sample taken 15 days post exposure. RNA isolated from the lymphocytes was used for preparation of scFv encoding repertoires for phage display. Sets of V-region primers were paired with constant region primers for heavy chain domain 1 IgG and IgM and light chain C-κ and C-λ and then linked in a scFv VH-VL orientation with a 15 amino acid spacer $(glycine_4\text{-}serine)_3$ [SEQ ID NO: 21] by overlap PCR [see J. D. Marks *et al.*, cited above, for description of the primers].

The resulting four scFv repertoires (V-κ with IgG and IgM, V-λ with IgG and IgM) were cloned into a phagemid vector similar to pHEN1 [H. R. Hoogenboom *et al.*, cited above] resulting in fusion of the scFvs to gene III of phage fd. The vector was then transformed into *E. coli* (e.g., strain TG1) by electroporation to yield the corresponding phagemid libraries.

Phage libraries displaying the scFv-gene 3 fusions were prepared by infection of each of the plasmid libraries with the M13K07 helper phage [R. H. Jackson, cited above] and were individually subjected to 2 rounds of panning against recombinant F-protein coated onto plastic. In the first round, 10^{11} phage in 2.5 ml phosphate buffered saline (PBS)/2% Marval™ non-fat dry

milk were incubated for 90 minutes in a tube coated with 5 μg/ml of F-protein [described in P. Tsui *et al*, J. Immunol., 157:772-780 (1996)] followed by 1 wash with 10x PBS/0.05% Tween 20 and a second wash with 10x PBS alone. Bound phage were eluted with 10 mM triethylamine and the eluate was neutralized with 1 M Tris-HCl, pH 7.4. The eluted phage were amplified and subjected to a similar second round of panning, except that the concentration of F-protein for coating was 2 μg/ml and the wash buffer contained 20x PBS.

E. coli were infected with the eluted phage and 96 colonies from each starting library were superinfected with helper phage and screened for F-protein binding activity. Only four positive clones were obtained from the 2 IgM libraries, whereas 41 positives were observed for the IgG libraries. By partial sequence analysis, all of the clones carried one of three different heavy chains. Complete sequences were obtained for the heavy and light chain V-regions for six clones, all from the IgG libraries.

Serial dilutions of titered phage stocks of each of these six clones were tested by ELISA for binding to recombinant F-protein and to RSV infected cell lysate. All showed binding to F-protein with the phage designated Gλ-1 showing the best activity. However, Gλ-1 and three other clones showed little binding to the RSV lysate.

Three clones: Gλ-1, Gλ-3 (lysate binding positive), and Gκ-1 (lysate binding negative), where "κ" and "λ" designate the class of the light chain, were characterized further for competition of their binding by F-protein specific neutralizing monoclonal antibodies, and their ability to inhibit virus

infection. The neutralizing mAbs RSV19 and B4 described in International patent publication No. WO92/04381, published March 19, 1992, and International patent publication No. WO93/20210, published October 14, 1993, recognize distinct epitopes on the F-protein. Gκ-1 was strongly inhibited by both antibodies. Gλ-1 was significantly inhibited by B4 only. Gκ-3 was not inhibited by either antibody (shown for Gλ-1 only; see Figs. 1A and 1B). In initial assays (Table I, experiments 1-3), all three clones showed neutralizing activity *in vitro*, with Gλ-1 being the most potent (Fig. 2, a graph of experiment 2), while control wild-type phage (M13K07) not displaying scFv had no effect.

To address the possibility that neutralization might result just from phage coating of virus, irrespective of epitope, a phage preparation of the non-neutralizing Fab 5-16 was tested in the same assay. In three out of four assays, this preparation also showed good neutralization activity, as did the control phage in two of these assays (Table I, experiments 4-7). This confounding observation of variable neutralization by both Fab 5-16 and control M13K07 phage rendered the viral neutralization studies inconclusive.

Table I

Phage Sample	Virus Neutralization (IC_{50} x 10^{-7})[1] (aru or kru/ml)[2]						
	Experiment #						
	1	2	3	4	5	6	7
Gκ-1 a	1,600		<300				
b				<10	<7		
Gλ-1 a		80	<300				
b				8.1	11		
c							120
Gλ-3 a		900	<300	180			
b					<7	10	
c							730
M13K07a			$>10^5$	$>10^5$		>5,000	
b					+all dil.	+all dil.	$>10^7$
Fab 5-19a				$>10^5$	40	180	
b							3.5

Legend:

[1] Assay according to M. J. Cannon, J. Virol. Meth., 16:293-301. Virus at 100 infectious centers/well was incubated with dilutions of the indicated phage for 1 hr and then added to susceptible cells for 3 hr. The virus/phage solution was aspirated and replaced with fresh medium and the cells were incubated overnight before peroxidase staining for virus infected cells.

[2] aru = ampicillin resistance units, a measure of phagmid containing particles.

kru = kanamycin resistance units, a measure of particles containing the phage genome (for the M13K07 control only).

In the face of these results, made more ambiguous by the dependence of all assays on phage stocks verses antibody proteins of known concentration, Gλ-1 was selected as the most likely candidate for a potent neutralizing antibody based on (1) its apparent better binding to F-protein, (2) its selective inhibition of binding by the B4 antibody, and (3) its suggested activity over background in the virus neutralization assay.

Example 2: Conversion of Gλ-1 scFV to mAb Version A

The DNA and encoded protein sequences of the VH and VL regions of Gλ-1 are shown in Figs. 3 [SEQ ID NOS: 1 and 2] and 4 [SEQ ID NOS: 3 and 4], respectively. For expression in mammalian cells, the heavy chain variable region and the light chain variable region from the Gλ-1 plasmid were cloned into derivatives of plasmid pCDN [Nambi, A. *et al.*, Mol. Cell. Biochem., 131:75-86 (1994)] in which the expression of the antibody chain is driven by the cytomegalovirus promoter (CMV) promoter. Plasmid pCD-HC68B is used for expressing full length heavy chains and plasmid pCN-HuLC, for expressing full length light chains.

In the initial constructs, changes in the sequence at the amino terminus were introduced by the PCR primers used for cloning the light chain and heavy chain variable regions from plasmid Gλ-1. In these constructs, the peptide signal sequence for both the heavy and light chains is derived from the Campath light chain [M. J. Page *et al.*, Biotechnology 9: 64-68 (1991)]. The heavy chain of Gλ-1 was PCR amplified from Gλ-1 phagemid DNA, using primers for the amino terminus and framework 4 of the variable region. The resulting

PCR fragment was cut with XhoI (site introduced by the amino terminus primer) and BstEII (naturally occurring site in framework 4), and cloned into an intermediate vector, F4HCV, at the XhoI/BstEII sites.

This cloning grafted the variable region of Gλ-1 onto the constant region of another anti-RSV heavy chain 194-F4 [cloned at SmithKline Beecham from a human hybridoma]. This intermediate clone was cut with XhoI and Bsp120I, and introduced into the same sites in pCD-HC68B. The XhoI site is introduced at the amino terminus by the PCR primer and, when cloned into pCD-HC68B at the same site is preceded in frame by the Campath leader sequence. The Bsp120I site is a naturally occurring, highly conserved sequence at the beginning of the C_{H-1} domain, and when cloned into pCD-HC68B at the same site, is in frame with the remaining sequence for the C_{H-1} through C_{H-3} regions of human IgG_1. In the resulting construct, Gλ-1Apcd (Figs. 8A-8F [SEQ ID NO: 13]), the amino acids immediately following the Campath leader are EVQLLE [SEQ ID NO: 17], where the residues LE are encoded by the nucleotide sequence for the XhoI cloning site.

The light chain of Gλ-1 was PCR amplified from the Gλ-1 phagemid DNA, using primers for the amino terminus and framework 4 of the variable region. The resulting PCR fragment was cut with SacI (site introduced by the amino terminus primer) and AvrII (naturally occurring site in framework 4), and cloned into 43-1pcn at the SacI/AvrII sites. This cloning grafted the variable region of Gλ-1, in frame, onto the constant region of another anti-RSV lambda light chain 43 [P. Tsui *et al.*, J. Immunol., 157: 772-780 (1996)], which had been cloned at SmithKline Beecham from a combinatorial library derived from RNA isolated from human spleen. The SacI

site is introduced at the amino terminus by the PCR primer and, when cloned into 43pcn at the same site, is preceded in frame by the Campath leader sequence. The first two amino acids of the mature light chain are therefore deleted. In the resulting construct, Gλ-1Apcn (Figs. 9A-9E [SEQ ID NO: 14]), the first two amino acids immediately following the leader are EL, where the residues EL are encoded by the nucleotide sequence for the SacI cloning site.

The nucleotide sequences of the plasmids Gλ-1Apcd and Gλ-1Apcn are shown in Figs. 8A-8F [SEQ ID NO: 13] and 9A-9E [SEQ ID NO: 14] respectively. This set of vectors was used to produce antibody Gλ-1A in COS cells and in CHO cells.

Example 3: Cloning Of The Corrected Gλ-1 Heavy and Light Chains

In cloning the variable region of the Gλ-1 heavy chain from the single chain Fv (scFv) format into the full length format, the fifth amino acid at the amino terminus was changed from Val to Leu, for cloning purposes. To correct this change, PCR primers were designed for the amino terminus of the Gλ-1 heavy chain cloned into pCD, which reverted the fifth amino acid back to Val. The correction was introduced via the PCR overlap technique using the correction primers and primers annealing to sequences within the CMV promoter and the C_{H-2} constant region as the outside 5' and 3' primers, respectfully. The final PCR product was digested with restriction enzymes, EcoRI and Bsp120I, and cloned into the Gλ-1Apcd vector at the same sites to create Gλ-1Bpcd.

The final construct was sequenced to verify that the amino terminus of the heavy chain had been corrected from EVQLLE [SEQ ID NO: 17] to EVQLVE [SEQ ID NO: 18] (see Fig 6). The nucleotide sequence of coding region for the corrected heavy chain, Gλ-1B, is shown in Figs. 10A-10B [SEQ ID NO: 15].

In cloning the variable region of the Gλ-1 light chain from the scFv format into the full length format, changes were introduced at the amino terminus for cloning purposes. Specifically, the first 2 amino acids (Gln and Ser) of the light chain were deleted and the third amino acid was changed from Val to Glu. To correct these changes, PCR primers were designed for the amino terminus of the Gλ-1 light chain cloned into pCN, which replaced the two deleted amino acids (Gln and Ser) and reverted the third amino acid back to Val. The corrections were introduced via the PCR overlap technique using the correction primers and primers annealing to sequences within the CMV promoter and the λ constant region as the outside 5' and 3' primers, respectfully. The final PCR product was digested with restriction enzymes, EcoRI and AvrII and cloned into the Gλ-1Apcn vector at the same sites to create Gλ-1Bpcn.

The final construct was sequenced to verify that the amino terminus of the light chain had been corrected from --EL to QSVL (amino acids 1-4 of SEQ ID NO: 10).

The nucleotide sequence of coding region for the corrected light chain, Gλ-1B, is shown in Fig. 11 [SEQ ID NO: 16]. This vector Gλ-1Bpcn, was used with Gλ-1Bpcd to produce antibody Gλ-1B, in COS cells and in CHO cells.

Example 4: Production of Gλ-1 mABs in Mammalian Cells

For initial characterization, the mAb constructs for each version, Gλ-1A heavy and light chain, Gλ-1B heavy and light chain, were expressed in COS cells essentially as described in Current Protocols in Molecular Biology, eds F. M. Ausubel *et al.*, 1988, John Wiley & Sons, vol. 1, section 9.1. On day 1 after the transfection, the culture growth medium was replaced with a serum-free medium [SmithKline Beecham] which was changed on day 3. Similar satisfactory results are obtained using a publicly available medium, DMEM supplemented with ITS™ Premix, an insulin, transferrin, selenium mixture (Collaborative Research, Bedford, MA) and 1 mg/ml bovine serum albumin (BSA).

The mAb was prepared from the day 3 + day 5 conditioned medium by standard protein A affinity chromatography methods (e.g., as described in Protocols in Molecular Biology) using, for example, Prosep A affinity resin (Bioprocessing Ltd., UK).

To produce larger quantities of the Gλ-1B mAB (100-200 mgs), the vectors were introduced into a proprietary CHO cell system. However, similar results will be obtained using $dhfr^-$ CHO cells as previously described [P. Hensley *et al.*, J. Biol. Chem., 269:23949-23958 (1994)]. Briefly, a total of 30 µg of linearized plasmid DNA (15 µg each of the A or B set of heavy chain and light chain vectors) is electroporated into $1x10^7$ cells. The cells are initially selected in nucleoside-free medium in 96 well plates. After three to four weeks, media from growth positive wells is screened for human immunoglobulin using an ELISA assay. The highest expressing colonies are expanded and selected in increasing concentrations of methotrexate for

amplification of the transfected vectors. The antibody is purified from conditioned medium by standard procedures using protein A affinity chromatography (Protein A sepharose, Pharmacia) followed by size exclusion chromatography (Superdex 200, Pharmacia).

The concentration and the antigen binding activity of the eluted antibody are measured by ELISA. The antibody containing fractions are pooled and further purified by size exclusion chromatography. As expected for any such antibody, by SDS-PAGE, the predominant protein product migrated at approximately 150 kd under non-reducing conditions and as two bands of 50 and 25 kd under reducing conditions. For antibody produced in CHO cells, the purity was > 90%, as judged by SDS-PAGE, and the concentration was accurately determined by amino acid analysis.

Example 5: Binding of the Gλ-1 mABs to recombinant F protein

Binding of the Gλ-1 mABs to recombinant F protein was measured in a standard solid phase ELISA. Antigen diluted in PBS pH 7.0 was adsorbed onto polystyrene round-bottom microplates (Dynatech, Immunolon II) for 18 hours. Wells were then aspirated and blocked with 0.5% boiled casein (BC) in PBS containing 1% Tween 20 (PBS/0.05% BC) for two hours. Antibodies (50 µl/well) were diluted to varying concentrations in PBS/0.5% BC containing 0.025% Tween 20 and incubated in antigen coated wells for one hour. Plates were washed three times with PBS containing 0.05% Tween 20, using a Titertek 320 microplate washer, followed by addition of HRP-labelled protein A/G (50 µl) diluted 1:5000. After washing three times, TMBlue substrate (TSI, #TM102) was added and plates were incubated an additional 15

minutes. The reaction was stopped by addition of 1 N H_2SO_4 and absorbance read at 450 nm using a Biotek ELISA reader.

The antigen binding epitope of the Gλ-1 mABs was examined in a competition ELISA. The Gλ-1 mABs were mixed with increasing concentrations of RSMU19 or B4, two potent neutralizing mAbs [Tempest *et al.*, Biotech., 9: 266-271 (1991); Kennedy *et al.*, J. Gen. Virol., 69: 3023-3032 (1988)] and added to F protein-coated wells. The epitope regions recognized by mAbs RSMU19 and B4 are quite distinct from each other as previously described in Arbiza et al., J. Gen. Virol., 73: 2225-2234 (1992). The concentration of the Gλ-1 mABs used in competition studies was determined previously to give 90% maximal binding to F antigen. Binding of the Gλ-1 mABs in the presence of other mABs was detected using HRP-labelled goat anti-human IgG. The reaction was developed as stated above.

The Gλ-1 mABs demonstrated potent binding to recombinant F (rF) protein by ELISA (EC_{50} for mAB B = 2.6 ng/ml). Binding of the Gλ-1 mABs to rF protein was inhibited by mAb B4, for which the F protein amino acids critical for antigen recognition are amino acids 268, 272 and 275 of SEQ ID NO: 20). Binding of the Gλ-1 mABs to rF protein was not inhibited by mAb RSMU19, for which F protein amino acid 429 of SEQ ID NO: 20 is critical for antigen recognition. These results indicate that residues in the region of amino acids 255-275 of the F protein [SEQ ID NO: 20] are critical for Gλ-1 mAB recognition.

Example 6: In vitro Fusion-Inhibition Activity of the Gλ-1 mABs

The ability of the Gλ-1 mABs to inhibit virus-induced cell fusion was determined using a modification of the *in vitro* microneutralization assay [Beeler *et al.*, J. Virol., 63:2941-2950 (1989)]. In this assay, 50 µl of RS Long strain virus (10-100 $TCID_{50}$/well [American Type Culture Collection ATCC VR-26] were mixed with 0.1 ml VERO cells ($5X10^3$/well) [ATCC CCL-81] in Minimum Essential Media (MEM) containing 2% fetal calf serum (FCS), for 4 hours at 37°C, 5% CO_2. Serial two-fold dilutions (in quadruplicate) of mAB (50 µl) were then added to wells containing virus-infected cells. Control cultures contained cells incubated with virus only (positive virus control) or cells incubated with media alone.

Cultures were incubated at 37°C in 5% CO_2 for 6 days at which time cytopathic effects (CPE) in virus control wells were > 90%. Microscopic examination for cytopathic effects were confirmed by ELISA. Media was aspirated from cultures and replaced with 50 µl of 90% methanol containing 0.6% H_2O_2. After 10 minutes, fixative was aspirated and plates were air dried overnight. Viral antigen was detected in the fixed cultures using 1 µg/ml biotinylated RSCHB4 (a human Fc derivative of the bovine B4 mAb [SmithKline Beecham]), followed by HRP-labelled streptavidin (Boehringer-Mannheim) diluted 1:10,000. The reaction was developed using TMBlue and stopped by addition of 1N H_2SO_4. Absorbance was measured at 450 nm ($O.D._{450}$).

Fusion-inhibition titers were defined as the concentration of antibody which caused a 50% reduction in ELISA signal (ED_{50}) as compared to virus controls.

Based on the curve generated in the ELISA by the standard virus titration, a 50% reduction in $O.D._{450}$ corresponded to $\geq$ 90% reduction in virus titer. Calculation of the 50% point was based on regression analysis of the dose titration.

The Gλ-1 mABs demonstrated potent *in vitro* fusion-inhibition activity against type A RS Long strain virus (ED_{50} for mAB B of 0.51 $\pm$ 0.38 μg/ml). In this *in vitro* fusion-inhibition assay, Gλ-1 mAB B was more active than the humanized mAB RSHZ19 (ED_{50} of 0.4-3.0 μg/ml) [Wyde *et al.*, Pediatr. Res., 38(4):543-550] in comparative assays.

Example 7: *In vivo* Activity of Gλ-1 mAB B: Prophylaxis and Therapy in Balb/c Mouse Model

Balb/c mice (5/group) were inoculated intraperitoneally with doses ranging from 0.06 mg/kg to 5 mg/kg of Gλ-1 mAB B either 24 hours prior (prophylaxis) or 4 days after (therapy) intranasal infection with 10^5 PFU of the A2 strain of human RSV. Mice were sacrificed 5 days after infection. Lungs were harvested and homogenized to determine virus titers.

Virus was undetectable in the lungs of mice treated prophylactically with $\geq$ 1.25 mg/kg Gλ-1 mAB B either prophylactically or therapeutically. See Table II below. Significant viral clearance (2-3 $\log_{10}$) was also achieved in animals receiving 0.31 mg/kg Gλ-1 mAB B either prophylactically or therapeutically.

Table II: Gλ-1 mAB B Prophylaxis and Therapy in Balb/c Mice

Treatment	Dose (mg/kg)	Lung Virus Titer (log_{10}/g lung) Prophylaxis	Therapy
Gλ-1 mAB B	5	<1.7	<1.7
	1.25	<1.7	<1.7
	0.31	1.8 ± 0.3	2.9 ± 0.4
	0.06	4.3 ± 0.7	4.5 ± 0.3
PBS	-	4.8 ± 0.7	4.7 ± 0.2

The Gλ-1 mABs have potent antiviral activity *in vitro* against a broad range of native RSV isolates of both type A and B, and show prophylactic and therapeutic efficacy *in vivo* in animal models. Thus, the Gλ-1 mABs are candidates for therapeutic, prophylactic, and diagnostic application in man.

Numerous modifications and variations of the present invention may be made by one of skill in the art in view of the invention described herein. Such modifications are believed to be encompassed by the specification and claims of the present invention. All references cited above are incorporated by reference herein.

WHAT IS CLAIMED IS:

1. A human monoclonal antibody and functional fragments thereof, specifically reactive with an F protein epitope of Respiratory Syncytial Virus and capable of neutralizing infection by said virus selected from the group consisting of Gλ-1A and Gλ-1B.

2. The monoclonal antibody according to Claim 1 which comprises the light chain amino acid sequence of Fig. 3 SEQ ID NO: 2 and the heavy chain amino acid sequence of Fig. 4 SEQ ID NO: 4.

3. The monoclonal antibody according to Claim 1 which comprises the light chain amino acid sequence encoded by the DNA sequence of Fig. 11 SEQ ID NO: 16 and the heavy chain amino acid sequence encoded by the DNA sequence of Figs. 10A-10B SEQ ID NO: 15.

4. The monoclonal antibody according to Claim 1 wherein said fragment is selected from the group consisting of Fv, Fab and $F(ab')_2$.

5. An isolated nucleic acid molecule selected from the group consisting of:

(a) a nucleic acid sequence encoding any of the human monoclonal antibodies, altered antibodies and CDRs of any of the claims 1-4;

(b) a nucleic acid complementary to any of the sequences in (a); and

(c) a nucleic acid sequence of 18 or more nucleotides capable of hybridizing to the CDRs of any of claims 1-4 under stringent conditions.

6. The isolated nucleic acid molecule according to Claim 5 comprising the sequences of Figs. 8A-8F and 9A-9E SEQ ID NOS: 13 and 14, or Figs. 10A-10B and 11 SEQ ID NOS: 15 and 16.

7. A recombinant plasmid comprising the nucleic acid sequences of any of Claims 5 or 6.

8. A host cell comprising the plasmid of Claim 7.

9. A process for the production of a human antibody specific for RSV comprising culturing the host cell of Claim 8 in a medium under suitable conditions of time temperature and pH and recovering the antibody so produced.

10. A method of detecting RSV comprising contacting a source suspected of containing RSV with a diagnostically effective amount of the monoclonal antibody of Claim 1 and determining whether the monoclonal antibody binds to the source.

11. A method for providing passive immunotherapy to RSV disease in a human, comprising administering to the human an immunotherapeutically effective amount of the monoclonal antibody of Claim 1.

12. The method according to Claim 11 wherein the passive immunotherapy is provided prophylactically.

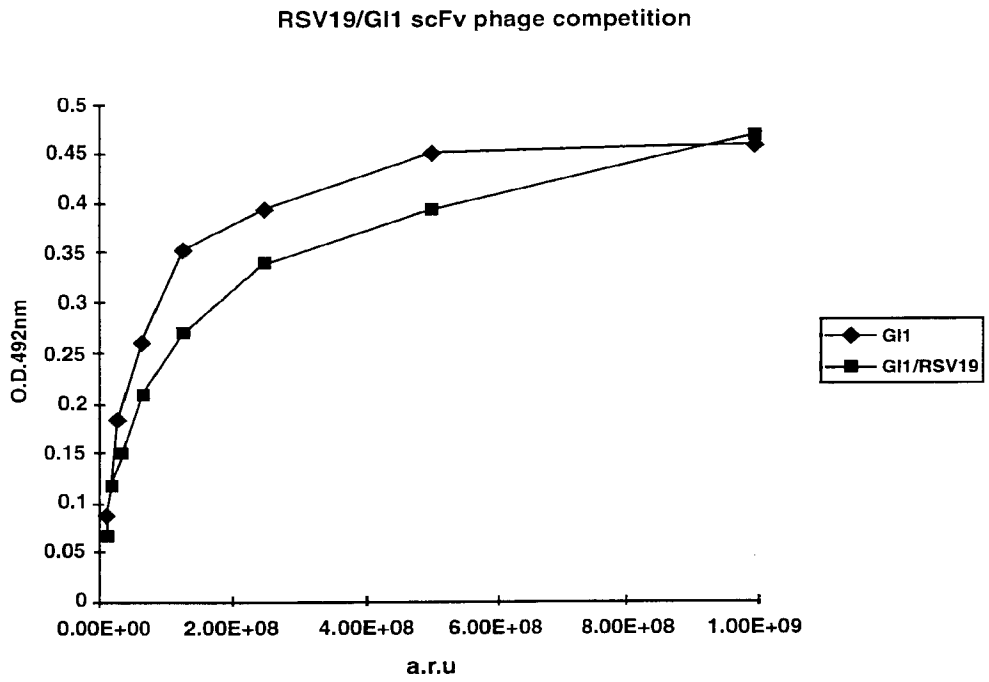
13. A pharmaceutical composition comprising at least one dose of an immunotherapeutically effective

amount of the monoclonal antibody of Claim 1 in a pharmaceutically acceptable carrier.

14. A pharmaceutical composition comprising at least one dose of an immunotherapeutically effective amount of the monoclonal antibody of Claim 1 in combination with at least one additional monoclonal antibody.

15. The pharmaceutical composition according to Claim 14 wherein said additional monoclonal antibody is an anti-RSV antibody distinguished from the antibody of Claim 1 by virtue of being reactive with a different epitope of the RSV F protein antigen.

Fig. 1A


RSV19/GI1 scFv phage competition
O.D.492nm
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0.00E+00
2.00E+08
4.00E+08
6.00E+08
8.00E+08
1.00E+09
a.r.u
GI1
GI1/RSV19

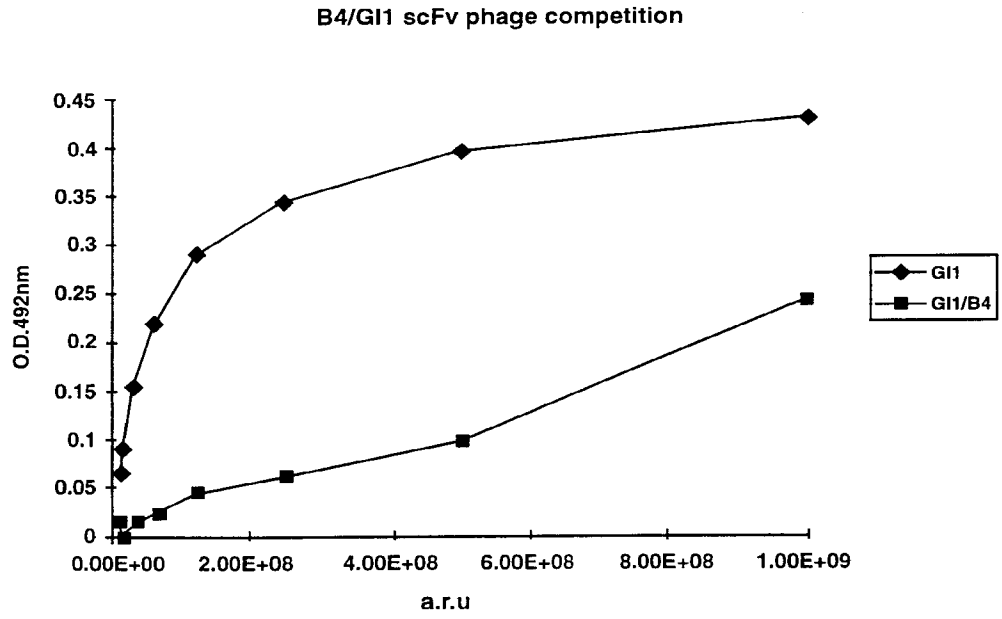

B4/GI1 scFv phage competition
O.D.492nm
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0.00E+00
2.00E+08
4.00E+08
6.00E+08
8.00E+08
1.00E+09
a.r.u
GI1
GI1/B4

Fig. 1B

Fig. 2

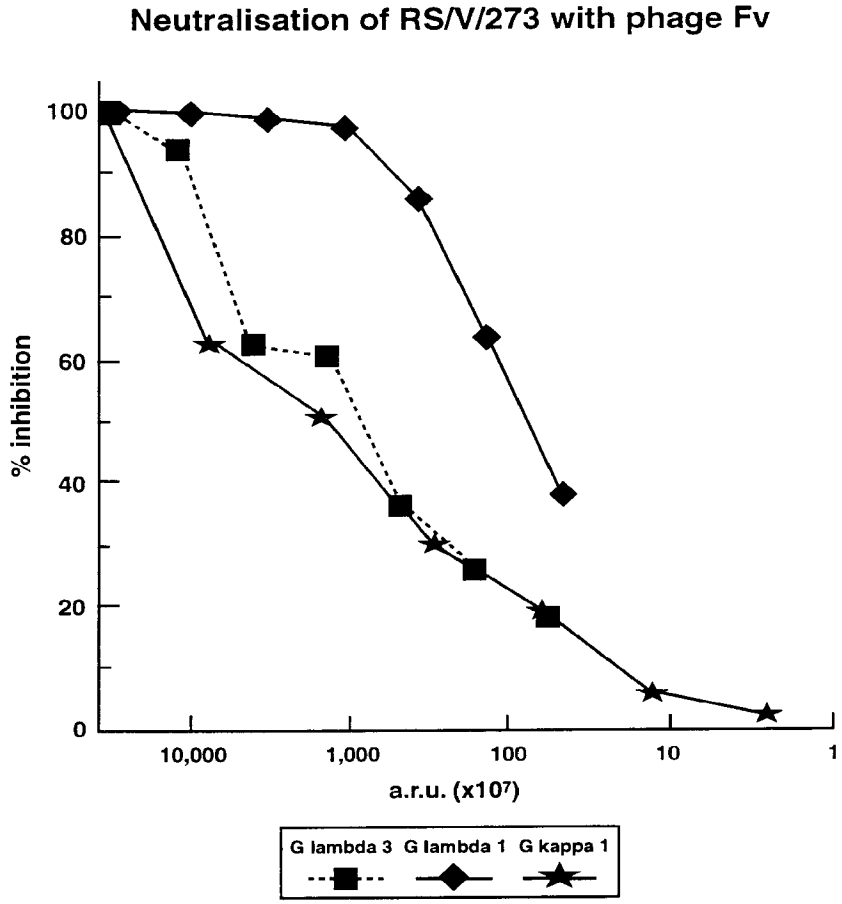

Neutralisation of RS/V/273 with phage Fv
100
80
60
40
20
0
% inhibition
10,000
1,000
100
10
1
a.r.u. (x10⁷)
G lambda 3
G lambda 1
G kappa 1

FIGURE 3

```
1   CAGTCTGTGTTGACGCAGCCGCCCTCAGTCTCTGCGGCCCCAGGACAGAA   50
    Q  S  V  L  T  Q  P  P  S  V  S  A  A  P  G  Q  K

51  GGTCACCATCTCCTGCACTGGGAGCAGCTCCAACCTCGGGGCAGGTTATG  100
     V  T  I  S  C  T  G  S  S  S  N  L  G  A  G  Y  D

101 ATGTTCACTGGTACCGGCAACTTCCAGGGACAGCCCCCAAACTCCTCATC  150
      V  H  W  Y  R  Q  L  P  G  T  A  P  K  L  L  I

151 TATGATAACAACAATCGGCCCTCAGGGGTCCCTGACCGATTCTCTGGCTC  200
    Y  D  N  N  N  R  P  S  G  V  P  D  R  F  S  G  S

201 CAAGTCTGGCCCCTCAGCCTCCCTGGCCATCTCTGGGCTCCAGGCTGAGG  250
     K  S  G  P  S  A  S  L  A  I  S  G  L  Q  A  E  D

251 ATGAGGCTGATTATTACTGCCAGTCCTATGACAGCAGCCTGAATGGTTAT  300
      E  A  D  Y  Y  C  Q  S  Y  D  S  S  L  N  G  Y

301 GTCTTCGGAACTGGGACCCAGCTCACCGTCCTAGGT                336
    V  F  G  T  G  T  Q  L  T  V  L  G
```

FIGURE 4

```
  1  GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTC   50
       E  V  Q  L  V  E  S  G  G  G  L  V  Q  P  G  G  S

 51  CCTGAGACTCTCCTGCGCAGCCTCTGGAGTCTCCCTCAGTGGATACAAGA  100
        L  R  L  S  C  A  A  S  G  V  S  L  S  G  Y  K  M

101  TGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAATGGGTCTCTTCC  150
        N  W  V  R  Q  A  P  G  K  G  L  E  W  V  S  S

151  ATTACTGGTATGAGTAATTACATACACTACTCAGACTCAGTGAAGGGCCG  200
        I  T  G  M  S  N  Y  I  H  Y  S  D  S  V  K  G  R

201  ATTCACCATCTCCAGAGACAACGCCATGAACTCACTGTATCTGCAAATGA  250
        F  T  I  S  R  D  N  A  M  N  S  L  Y  L  Q  M  N

251  ACAGCCTGACAGCCGAGGACACGGGTGTTTATTATTGTGCGACACAACCG  300
        S  L  T  A  E  D  T  G  V  Y  Y  C  A  T  Q  P

301  GGGGAGCTGGCGCCTTTTGACCATTGGGGCCAGGGAACCCTGGTCACCGT  350
        G  E  L  A  P  F  D  H  W  G  Q  G  T  L  V  T  V

351  CTCCTCA                                             357
        S  S
```

Figure 5

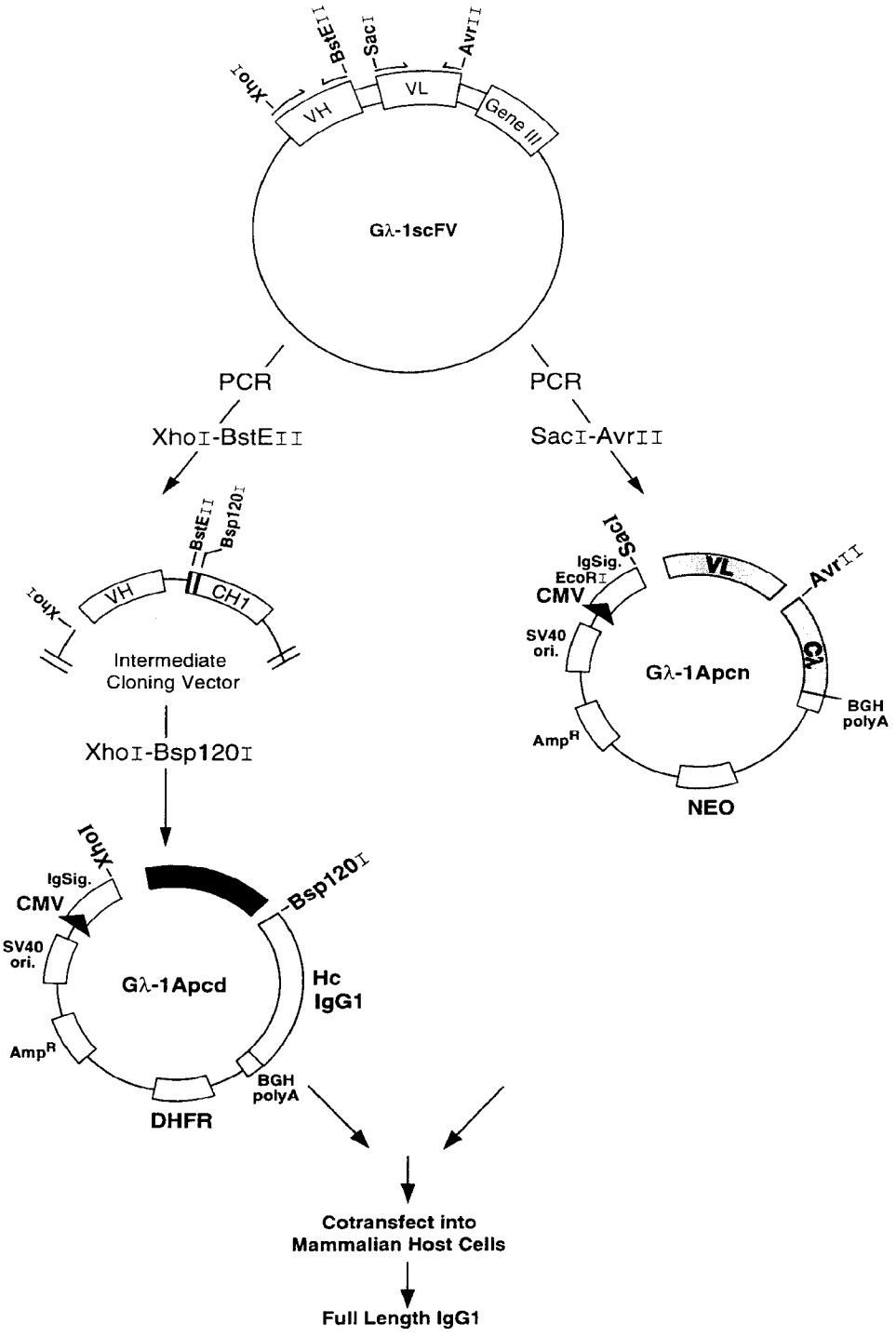

XhoI
BstEII
SacI
AvrII
VH
VL
Gene III
Gλ-1scFV
PCR
XhoI-BstEII
PCR
SacI-AvrII
BstEII
Bsp120I
VH
CH1
Intermediate
Cloning Vector
XhoI-Bsp120I
SacI
IgSig.
EcoRI
CMV
VL
AvrII
SV40
ori.
Gλ-1Apcn
CL
BGH
polyA
AmpR
NEO
XhoI
IgSig.
CMV
Bsp120I
SV40
ori.
Gλ-1Apcd
Hc
IgG1
AmpR
BGH
polyA
DHFR
Cotransfect into
Mammalian Host Cells
Full Length IgG1

FIGURE 6

Comparison of the Heavy Chain Amino Acid Sequences of the Gλ-1 single chain fv and mAbs

Leader and Variable Regions

```
GL Dp58:                              EVQLVESGGGLVQPGGSLRLSCAASGFTFS
Gλ-1 scFv:                            ---------------------------VSL-
Gλ-1A:        MGWSCIILFLVATATGVHS----L-------------------------
Gλ-1B:        ----------------------V-------------------------

              CDR1                          CDR2
              -----                         ----------------
GL Dp58:      SYEMNWVRQAPGKGLEWVSYISSSGSTIYYADSVKGRFTISRDNAKNSLY
Gλ-1 scFV:    G-K---------------S-TGMSNY-H-S--------------M----
Gλ-1A:        ------------------------------------------------
Gλ-1B:        ------------------------------------------------

                                  CDR3
                                  ---------
GL: Dp58:     LQMNSLRAEDTAVYYCAR
Gλ-1 scFv:    ------T----G-----TQPGELAPFDHWGQGTLVTVSS
Gλ-1A:        ---------------------------------------
Gλ-1B:        ---------------------------------------
```

FIG 7

Comparison of the Light Chain Amino Acid Sequences of the Gλ-1A: single chain Fv and mAbs

Leader and Variable Regions

```
                                                                CDR1
                                                               --------
GL DpL8:                          QSVLTQPPSVSGAPGQRVTISCTGSSSNIG
Gλ-1 scFv:                        -----------A----K-----------L-
Gλ-1A:      MGWSCIILFLVATATGVHS  E-------------------------------
Gλ-1B:      --------------------QSV-----------------------------

                                  CDR2
            ------                --------
GL DpL8:    AGYDVHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAITGL
Gλ-1scFv:   --------R------------D-N----------------P------S--
Gλ-1A:      ------------------------------------------------------
Gλ-1B:      ------------------------------------------------------

                       CDR3
                      -----------
GL DpL8:    QAEDEADYYC
Gλ-1 scFv:  ----------QSYDSSLNGYVFGTGTQLTVLG
Gλ-1A:      --------------------------------
Gλ-1B:      --------------------------------
```

FIGURE 8A

```
   1  gacgtcgcggccgctctaggcctccaaaaaagcctcctcactacttctgg

  51  aatagctcagaggccgaggcggcctcggcctctgcataaataaaaaaaat

 101  tagtcagccatgcatggggcggagaatgggcggaactgggcggagttagg

 151  ggcgggatgggcggagttaggggcgggactatggttgctgactaattgag

 201  atgcatgctttgcatacttctgcctgctggggagcctggggactttccac

 251  acctggttgctgactaattgagatgcatgctttgcatacttctgcctgct

 301  ggggagcctggggactttccacaccctaactgacacacattccacagaat

 351  taattccccggggatcgatccgtcgacgtacgactagttattaatagtaat

 401  caattacggggtcattagttcatagcccatatatggagttccgcgttaca

 451  taacttacggtaaatggcccgcctggctgaccgcccaacgacccccgccc

 501  attgacgtcaataatgacgtatgttcccatagtaacgccaatagggactt

 551  tccattgacgtcaatgggtggactatttacggtaaactgcccacttggca

 601  gtacatcaagtgtatcatatgccaagtacgcccctattgacgtcaatga

 651  cggtaaatggcccgcctggcattatgcccagtacatgaccttatgggact

 701  ttcctacttggcagtacatctacgtattagtcatcgctattaccatggtg

 751  atgcggttttggcagtacatcaatgggcgtggatagcggtttgactcacg

 801  gggatttccaagtctccaccccattgacgtcaatgggagtttgttttggc

 851  accaaaatcaacgggactttccaaaatgtcgtaacaactccgccccattg

 901  acgcaaatgggcggtaggcgtgtacggtgggaggtctatataagcagagc

                                                  EcoRI
 951  tgggtacgtgaaccgtcagatcgcctggagacgccatcgaattctgagca

1001  cacaggacctcaccatgggatggagctgtatcatcctcttcttggtagca
                    M  G  W  S  C  I  I  L  F  L  V  A
                    Leader start

                                                 XhoI
1051  acagctacaggtgtccactccgaggtccaactgctcgagtctgggggagg
       T  A  T  G  V  H  S  E  V  Q  L  L  E  S---
                           Processed N-term
```

FIGURE 8B

```
1101  cttggtacagcctgggggggtccctgagactctcctgcgcagcctctggag

1151  tctccctcagtggatacaagatgaactgggtccgccaggctccagggaag

1201  gggctggaatgggtctcttccattactggtatgagtaattacatacacta

1251  ctcagactcagtgaagggccgattcaccatctccagagacaacgccatga

1301  actcactgtatctgcaaatgaacagcctgacagccgaggacacgggtgtt

1351  tattattgtgcgacacaaccgggggagctggcgcctttgaccattgggg

                    BstEII                          Bsp120I
1401  ccagggaaccctggtcaccgtctcctcagcctccaccaagggcccatcgg
       Q  G  T  L  V  T  V  S  S /
                framework IV / CH1

1451  tcttccccctggcaccctcctccaagagcacctctgggggcacagcggcc

1501  ctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtg

1551  gaactcaggcgccctgaccagcggcgtgcacaccttcccggctgtcctac

                                          BstEII
1601  agtcctcaggactctactccctcagcagcgtggtgaccgtgccctccagc

1651  agcttgggcacccagacctacatctgcaacgtgaatcacaagcccagcaa

1701  caccaaggtggacaagaaagttgagcccaaatcttgtgacaaaactcaca

1751  catgcccaccgtgcccagcacctgaactcctgggggggaccgtcagtcttc

1801  ctcttcccccccaaaacccaaggacaccctcatgatctcccggacccctga

1851  ggtcacatgcgtggtggtggacgtgagccacgaagaccctgaggtcaagt

1901  tcaactggtacgtggacggcgtggaggtgcataatgccaagacaaagccg

1951  cgggaggagcagtacaacagcacgtaccgggtggtcagcgtcctcaccgt

2001  cctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctcca

2051  acaaagccctcccagcccccatcgagaaaaccatctccaaagccaaaggg

2101  cagccccgagaaccacaggtgtacaccctgcccccatcccgggatgagct

2151  gaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatccca
```

FIGURE 8C

2201 gcgacatcgccgtggagtgggagagcaatgggcagccggagaacaactac

2251 aagaccacgcctcccgtgctggactccgacggctccttcttcctctacag

2301 caagctcaccgtggacaagagcaggtggcagcaggggaacgtcttctcat

2351 gctccgtgatgcatgaggctctgcacaaccactacacgcagaagagcctc

2401 tccctgtctccgggtaaatgatagatatctacgtatgatcagcctcgact
S P G K * C-term of heavy chain

2451 gtgccttctagttgccagccatctgttgtttgcccctccccgtgccttc

2501 cttgaccctggaaggtgccactcccactgtcctttcctaataaaatgagg

2551 aaattgcatcgcattgtctgagtaggtgtcattctattctgggggggtggg

2601 gtggggcaggacagcaaggggaggattgggaagacaatagcaggcatgc

2651 tggggatgcggtgggctctatggaaccagctggggctcgacagcgctgga

2701 tctcccgatccccagctttgcttctcaatttcttatttgcataatgagaa

2751 aaaaaggaaaattaattttaacaccaattcagtagttgattgagcaaatg

2801 cgttgccaaaaaggatgctttagagacagtgttctctgcacagataagga

2851 caaacattattcagagggagtacccagagctgagactcctaagccagtga

2901 gtggcacagcattctagggagaaatatgcttgtcatcaccgaagcctgat

2951 tccgtagagccacaccttggtaagggccaatctgctcacacaggatagag

3001 agggcaggagccagggcagagcatataaggtgaggtaggatcagttgctc

3051 ctcacatttgcttctgacatagttgtgttgggagcttggatagcttggac

3101 agctcagggctgcgatttcgcgccaaacttgacggcaatcctagcgtgaa

3151 ggctggtaggattttatccccgctgccatcatggttcgaccattgaactg

3201 catcgtcgccgtgtcccaaaatatggggattggcaagaacggagacctac

3251 cctggcctccgctcaggaacgagttcaagtacttccaaagaatgaccaca

3301 acctcttcagtggaaggtaaacagaatctggtgattatgggtaggaaaac

3351 ctggttctccattcctgagaagaatcgacctttaaaggacagaattaata

FIGURE 8D

3401 tagttctcagtagagaactcaaagaaccaccacgaggagctcattttctt

3451 gccaaaagtttggatgatgccttaagacttattgaacaaccggaattggc

3501 aagtaaagtagacatggtttggatagtcggaggcagttctgtttaccagg

3551 aagccatgaatcaaccaggccaccttagactctttgtgacaaggatcatg

3601 caggaatttgaaagtgacacgtttttcccagaaattgatttggggaaata

3651 taaacttctcccagaatacccaggcgtcctctctgaggtccaggaggaaa

3701 aaggcatcaagtataagtttgaagtctacgagaagaaagactaacaggaa

3751 gatgctttcaagttctctgctcccctcctaaagctatgcatttttataag

3801 accatgggacttttgctggctttagatcagcctcgactgtgccttctagt

3851 tgccagccatctgttgtttgcccctcccccgtgccttccttgaccctgga

3901 aggtgccactcccactgtcctttcctaataaaatgaggaaattgcatcgc

3951 attgtctgagtaggtgtcattctattctgggggggtggggtggggcaggac

4001 agcaaggggaggattgggaagacaatagcaggcatgctggggatgcggt

4051 gggctctatggaaccagctggggctcgatcgagtgtatgactgcggccgc

4101 gatcccgtcgagagcttggcgtaatcatggtcatagctgtttcctgtgtg

4151 aaattgttatccgctcacaattccacacaacatacgagccggaagcataa

4201 agtgtaaagcctggggtgcctaatgagtgagctaactcacattaattgcg

4251 ttgcgctcactgcccgctttccagtcgggaaacctgtcgtgccagctgca

4301 ttaatgaatcggccaacgcgcggggagaggcggtttgcgtattgggcgct

4351 cttccgcttcctcgctcactgactcgctgcgctcggtcgttcggctgcgg

4401 cgagcggtatcagctcactcaaaggcggtaatacggttatccacagaatc

4451 aggggataacgcaggaaagaacatgtgagcaaaaggccagcaaaaggcca

4501 ggaaccgtaaaaaggccgcgttgctggcgtttttccataggctccgcccc

4551 cctgacgagcatcacaaaaatcgacgctcaagtcagaggtggcgaaaccc

4601 gacaggactataaagataccaggcgtttcccccctggaagctccctcgtgc

FIGURE 8E

4651 gctctcctgttccgaccctgccgcttaccggatacctgtccgcctttctc

4701 ccttcgggaagcgtggcgctttctcaatgctcacgctgtaggtatctcag

4751 ttcggtgtaggtcgttcgctccaagctgggctgtgtgcacgaacccccg

4801 ttcagcccgaccgctgcgccttatccggtaactatcgtcttgagtccaac

4851 ccggtaagacacgacttatcgccactggcagcagccactggtaacaggat

4901 tagcagagcgaggtatgtaggcggtgctacagagttcttgaagtggtggc

4951 ctaactacggctacactagaaggacagtatttggtatctgcgctctgctg

5001 aagccagttaccttcggaaaaagagttggtagctcttgatccggcaaaca

5051 aaccaccgctggtagcggtggtttttttgtttgcaagcagcagattacgc

5101 gcagaaaaaaaggatctcaagaagatcctttgatcttttctacggggtct

5151 gacgctcagtggaacgaaaactcacgttaagggattttggtcatgagatt

5201 atcaaaaaggatcttcacctagatccttttaaattaaaaatgaagtttta

5251 aatcaatctaaagtatatatgagtaaacttggtctgacagttaccaatgc

5301 ttaatcagtgaggcacctatctcagcgatctgtctatttcgttcatccat

5351 agttgcctgactccccgtcgtgtagataactacgatacgggagggcttac

5401 catctggccccagtgctgcaatgataccgcgagacccacgctcaccggct

5451 ccagatttatcagcaataaaccagccagccggaagggccgagcgcagaag

5501 tggtcctgcaactttatccgcctccatccagtctattaattgttgccggg

5551 aagctagagtaagtagttcgccagttaatagtttgcgcaacgttgttgcc

5601 attgctacaggcatcgtggtgtcacgctcgtcgtttggtatggcttcatt

5651 cagctccggttcccaacgatcaaggcgagttacatgatccccccatgttgt

5701 gcaaaaaagcggttagctccttcggtcctccgatcgttgtcagaagtaag

5751 ttggccgcagtgttatcactcatggttatggcagcactgcataattctct

5801 tactgtcatgccatccgtaagatgcttttctgtgactggtgagtactcaa

FIGURE 8F

5851 ccaagtcattctgagaatagtgtatgcggcgaccgagttgctcttgcccg

5901 gcgtcaatacgggataataccgcgccacatagcagaactttaaaagtgct

5951 catcattggaaaacgttcttcggggcgaaaactctcaaggatcttaccgc

6001 tgttgagatccagttcgatgtaacccactcgtgcacccaactgatcttca

6051 gcatcttttactttcaccagcgtttctgggtgagcaaaaacaggaaggca

6101 aaatgccgcaaaaaagggaataagggcgacacggaaatgttgaatactca

6151 tactcttccttttcaatattattgaagcatttatcagggttattgtctc

6201 atgagcggatacatatttgaatgtatttagaaaaataaacaaataggggt

6251 tccgcgcacatttccccgaaaagtgccacct

FIGURE 9A

```
   1  gacgtcgcggccgctctaggcctccaaaaaagcctcctcactacttctgg
  51  aatagctcagaggccgaggcggcctcggcctctgcataaataaaaaaaat
 101  tagtcagccatgcatggggcggagaatgggcggaactgggcggagttagg
 151  ggcgggatgggcggagttaggggcgggactatggttgctgactaattgag
 201  atgcatgctttgcatacttctgcctgctggggagcctggggactttccac
 251  acctggttgctgactaattgagatgcatgctttgcatacttctgcctgct
 301  ggggagcctggggactttccacaccctaactgacacacattccacagaat
 351  taattccccggggatcgatccgtcgacgtacgactagttattaatagtaat
 401  caattacggggtcattagttcatagcccatatatggagttccgcgttaca
 451  taacttacggtaaatggcccgcctggctgaccgcccaacgacccccgccc
 501  attgacgtcaataatgacgtatgttcccatagtaacgccaatagggactt
 551  tccattgacgtcaatgggtggactatttacggtaaactgcccacttggca
 601  gtacatcaagtgtatcatatgccaagtacgccccctattgacgtcaatga
 651  cggtaaatggcccgcctggcattatgcccagtacatgaccttatgggact
 701  ttcctacttggcagtacatctacgtattagtcatcgctattaccatggtg
 751  atgcggttttggcagtacatcaatgggcgtggatagcggtttgactcacg
 801  gggatttccaagtctccaccccattgacgtcaatgggagtttgttttggc
 851  accaaaatcaacgggactttccaaaatgtcgtaacaactccgccccattg
 901  acgcaaatgggcggtaggcgtgtacggtgggaggtctatataagcagagc
                                                  EcoRI
 951  tgggtacgtgaaccgtcagatcgcctggagacgccatcgaattctgagca
1001  cacaggacctcaccatgggatggagctgtatcatcctcttcttggtagca
                      M  G  W  S  C  I  I  L  F  L  V  A
                      Leader start
                                  SacI
1051  acagctacaggtgtccactccgagctcacgcagccgccctcagtctctgc
       T  A  T  G  V  H  S  E  L  T  Q --
                             Processed N-term
```

FIGURE 9B

1101 ggccccaggacagaaggtcaccatctcctgcactgggagcagctccaacc

1151 tcggggcaggttatgatgttcactggtaccggcaacttccagggacagcc

1201 cccaaactcctcatctatgataacaacaatcggccctcaggggtccctga

1251 ccgattctctggctccaagtctggccctcagcctccctggccatctctg

1301 ggctccaggctgaggatgaggctgattattactgccagtcctatgacagc

AvrII

1351 agcctgaatggttatgtcttcggaactgggacccagctcaccgtcctagg

T Q L T V L G

Framework IV / Cλ

1401 tcagcccaaggctgcccctcggtcactctgttcccgccctcctctgagg

1451 agcttcaagccaacaaggccacactggtgtgtctcataagtgacttctac

1501 ccgggagccgtgacagtggcctggaaggcaattagcagccccgtcaaggc

1551 gggagtggagaccaccacaccctccaaacaaagcaacaacaagtacgcgg

1601 ccagcagctatctgagcctgacgcctgagcagtggaagtcccacagaagg

1651 tacagctgccaggtcacgcatgaagggagcaccgtggagaagacagtggc

1701 ccctacagaatgttcatagttctagatctacgtatgatcagcctcgactg

P T E C S * C-term light chain

1751 tgccttctagttgccagccatctgttgtttgcccctcccccgtgccttcc

1801 ttgaccctggaaggtgccactcccactgtcctttcctaataaaatgagga

1851 aattgcatcgcattgtctgagtaggtgtcattctattctgggggggtgggg

1901 tggggcaggacagcaagggggaggattgggaagacaatagcaggcatgct

1951 ggggatgcggtgggctctatggaaccagctggggctcgacagctcgagct

2001 agctttgcttctcaatttcttatttgcataatgagaaaaaaaggaaaatt

2051 aattttaacaccaattcagtagttgattgagcaaatgcgttgccaaaaag

2101 gatgctttagagacagtgttctctgcacagataaggacaaacattattca

2151 gagggagtacccagagctgagactcctaagccagtgagtggcacagcatt

FIGURE 9C

2201 ctagggagaaatatgcttgtcatcaccgaagcctgattccgtagagccac

2251 accttggtaagggccaatctgctcacacaggatagagagggcaggagcca

2301 gggcagagcatataaggtgaggtaggatcagttgctcctcacatttgctt

2351 ctgacatagttgtgttgggagcttggatcgatccaccatggttgaacaag

2401 atggattgcacgcaggttctccggccgcttgggtggagaggctattcggc

2451 tatgactgggcacaacagacaatcggctgctctgatgccgccgtgttccg

2501 gctgtcagcgcaggggcgcccggttctttttgtcaagaccgacctgtccg

2551 gtgccctgaatgaactgcaggacgaggcagcgcggctatcgtggctggcc

2601 acgacgggcgttccttgcgcagctgtgctcgacgttgtcactgaagcggg

2651 aagggactggctgctattgggcgaagtgccggggcaggatctcctgtcat

2701 ctcaccttgctcctgccgagaaagtatccatcatggctgatgcaatgcgg

2751 cggctgcatacgcttgatccggctacctgcccattcgaccaccaagcgaa

2801 acatcgcatcgagcgagcacgtactcggatggaagccggtcttgtcgatc

2851 aggatgatctggacgaagagcatcaggggctcgcgccagccgaactgttc

2901 gccaggctcaaggcgcgcatgcccgacggcgaggatctcgtcgtgaccca

2951 tggcgatgcctgcttgccgaatatcatggtggaaaatggccgcttttctg

3001 gattcatcgactgtggccggctgggtgtggcggaccgctatcaggacata

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3151 ccttctatcgccttcttgacgagttcttctgagcgggactctggggttcg

3201 aaatgaccgaccaagcgacgcccaacctgccatcacgagatttcgattcc

3251 accgccgccttctatgaaaggttgggcttcggaatcgttttccgggacgc

3301 cggctggatgatcctccagcgcggggatctcatgctggagttcttcgccc

3351 accccaacttgtttattgcagcttataatggttacaaataaagcaatagc

FIGURE 9D

3401 atcacaaatttcacaaataaagcatttttttcactgcattctagttgtgg

3451 tttgtccaaactcatcaatgtatcttatcatgtctggatcggccgcga

3501 tcccgtcgagagcttggcgtaatcatggtcatagctgtttcctgtgtgaa

3551 attgttatccgctcacaattccacacaacatacgagccggaagcataaag

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3701 aatgaatcggccaacgcgcggggagaggcggtttgcgtattgggcgctct

3751 tccgcttcctcgctcactgactcgctgcgctcggtcgttcggctgcggcg

3801 agcggtatcagctcactcaaaggcggtaatacggttatccacagaatcag

3851 gggataacgcaggaaagaacatgtgagcaaaaggccagcaaaaggccagg

3901 aaccgtaaaaaggccgcgttgctggcgtttttccataggctccgcccccc

3951 tgacgagcatcacaaaaatcgacgctcaagtcagaggtggcgaaacccga

4001 caggactataaagataccaggcgtttcccccctggaagctccctcgtgcgc

4051 tctcctgttccgaccctgccgcttaccggatacctgtccgcctttctccc

4101 ttcgggaagcgtggcgctttctcaatgctcacgctgtaggtatctcagtt

4151 cggtgtaggtcgttcgctccaagctgggctgtgtgcacgaaccccccgtt

4201 cagcccgaccgctgcgccttatccggtaactatcgtcttgagtccaaccc

4251 ggtaagacacgacttatcgccactggcagcagccactggtaacaggatta

4301 gcagagcgaggtatgtaggcggtgctacagagttcttgaagtggtggcct

4351 aactacggctacactagaaggacagtatttggtatctgcgctctgctgaa

4401 gccagttaccttcggaaaaagagttggtagctcttgatccggcaaacaaa

4451 ccaccgctggtagcggtggtttttttgtttgcaagcagcagattacgcgc

4501 agaaaaaaaggatctcaagaagatcctttgatcttttctacggggtctga

4551 cgctcagtggaacgaaaactcacgttaagggattttggtcatgagattat

FIGURE 9E

4601 caaaaaggatcttcacctagatccttttaaattaaaaatgaagttttaaa

4651 tcaatctaaagtatatatgagtaaacttggtctgacagttaccaatgctt

4701 aatcagtgaggcacctatctcagcgatctgtctatttcgttcatccatag

4751 ttgcctgactccccgtcgtgtagataactacgatacgggagggcttacca

4801 tctggccccagtgctgcaatgataccgcgagacccacgctcaccggctcc

4851 agatttatcagcaataaaccagccagccggaagggccgagcgcagaagtg

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5001 tgctacaggcatcgtggtgtcacgctcgtcgtttggtatggcttcattca

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5251 aagtcattctgagaatagtgtatgcggcgaccgagttgctcttgcccggc

5301 gtcaatacgggataataccgcgccacatagcagaactttaaaagtgctca

5351 tcattggaaaacgttcttcggggcgaaaactctcaaggatcttaccgctg

5401 ttgagatccagttcgatgtaacccactcgtgcacccaactgatcttcagc

5451 atcttttactttcaccagcgtttctgggtgagcaaaaacaggaaggcaaa

5501 atgccgcaaaaaagggaataagggcgacacggaaatgttgaatactcata

5551 ctcttcctttttcaatattattgaagcatttatcagggttattgtctcat

5601 gagcggatacatatttgaatgtatttagaaaaataaacaaatagggggttc

5651 cgcgcacatttccccgaaaagtgccacct

FIGURE 10A

EcoRI
gaattctgagca 1000

cacaggacctcaccatgggatggagctgtatcatcctcttcttggtagca 1050
M G W S C I I L F L V A

acagctacaggtgtccactccgaggtgcagctggtggagtctgggggagg 1100
T A T G V H S E V Q L V E S -
N-term

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gggctggaatgggtctcttccattactggtatgagtaattacatacacta 1250

ctcagactcagtgaagggccgattcaccatctccagagacaacgccatga 1300

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Bsp120I
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cgggaggagcagtacaacagcacgtaccgggtggtcagcgtcctcaccgt 2000

cctgcaccaggactggctgaatggcaaggagtacaagtgcaaggtctcca 2050

FIGURE 10B

acaaagccctcccagcccccatcgagaaaaccatctccaaagccaaaggg 2100

cagccccgagaaccacaggtgtacaccctgcccccatcccgggatgagct 2150

gaccaagaaccaggtcagcctgacctgcctggtcaaaggcttctatccca 2200

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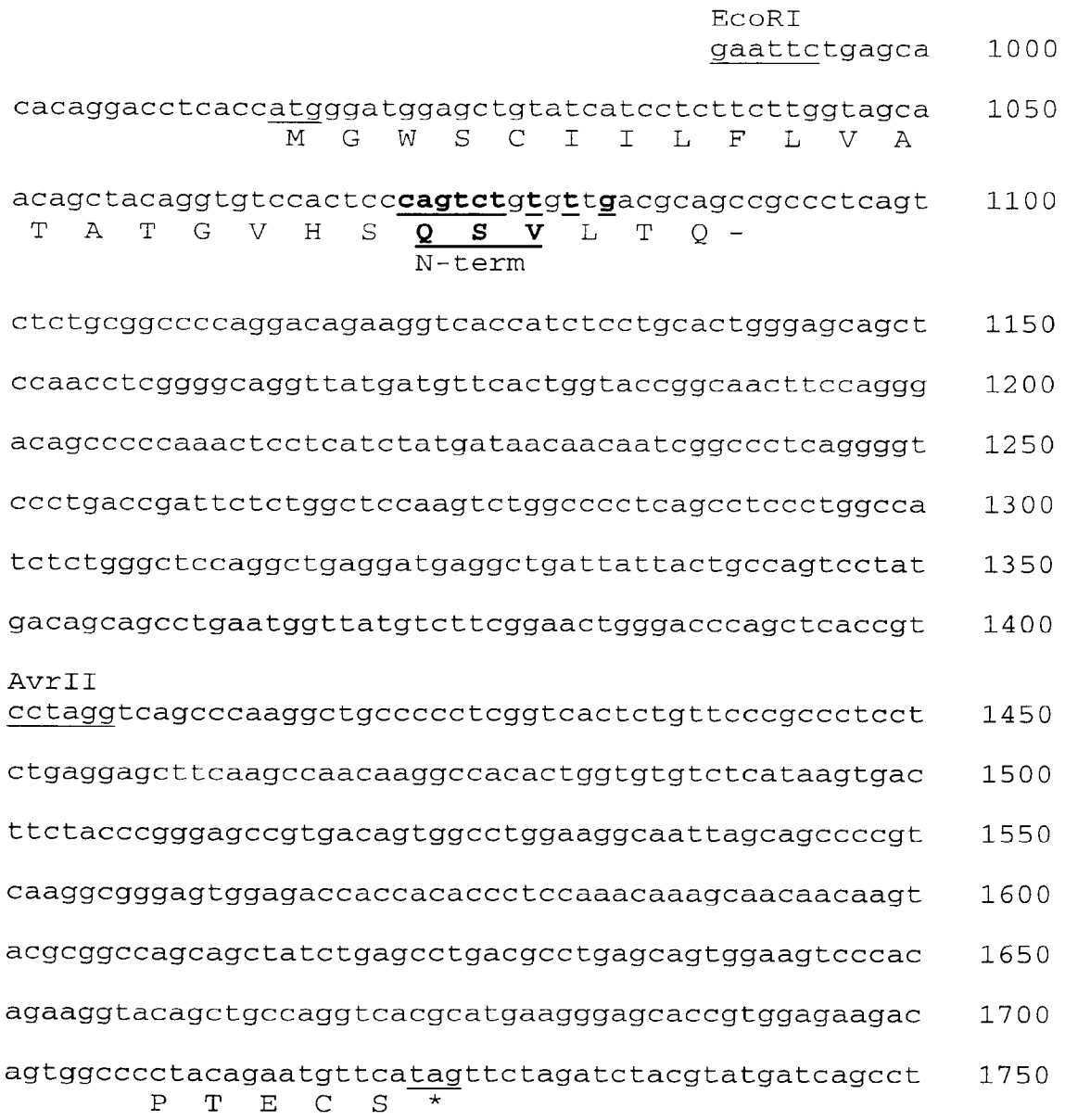
S P G K *

FIGURE 11


EcoRI
gaattctgagca 1000
cacaggacctcaccatgggatggagctgtatcatcctcttcttggtagca 1050
M G W S C I I L F L V A
acagctacaggtgtccactccagtctgtgttgacgcagccgccctcagt 1100
T A T G V H S Q S V L T Q -
N-term
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agaaggtacagctgccaggtcacgcatgaagggagcaccgtggagaagac 1700
agtggcccctacagaatgttcatagttctagatctacgtatgatcagcct 1750
P T E C S *

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: SmithKline Beecham, PLC

(ii) TITLE OF INVENTION: Human Monoclonal Antibody

(iii) NUMBER OF SEQUENCES: 21

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: SmithKline Beecham Corporation
(B) STREET: 709 Swedeland Road
(C) CITY: King of Prussia
(D) STATE: PA
(E) COUNTRY: USA
(F) ZIP: 19406-2799

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: GB
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: King, William T.
(B) REGISTRATION NUMBER: 30,954
(C) REFERENCE/DOCKET NUMBER: #

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 610-270-4800
(B) TELEFAX: 610-270-4026

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 336 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..336

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```
CAG TCT GTG TTG ACG CAG CCG CCC TCA GTC TCT GCG GCC CCA GGA CAG        48
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln
 1               5                  10                  15

AAG GTC ACC ATC TCC TGC ACT GGG AGC AGC TCC AAC CTC GGG GCA GGT        96
```

```
Lys Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Leu Gly Ala Gly
            20                  25                  30

TAT GAT GTT CAC TGG TAC CGG CAA CTT CCA GGG ACA GCC CCC AAA CTC      144
Tyr Asp Val His Trp Tyr Arg Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

CTC ATC TAT GAT AAC AAC AAT CGG CCC TCA GGG GTC CCT GAC CGA TTC      192
Leu Ile Tyr Asp Asn Asn Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

TCT GGC TCC AAG TCT GGC CCC TCA GCC TCC CTG GCC ATC TCT GGG CTC      240
Ser Gly Ser Lys Ser Gly Pro Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

CAG GCT GAG GAT GAG GCT GAT TAT TAC TGC CAG TCC TAT GAC AGC AGC      288
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
                85                  90                  95

CTG AAT GGT TAT GTC TTC GGA ACT GGG ACC CAG CTC ACC GTC CTA GGT      336
Leu Asn Gly Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu Gly
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 112 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln
 1               5                  10                  15

Lys Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Leu Gly Ala Gly
            20                  25                  30

Tyr Asp Val His Trp Tyr Arg Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Asp Asn Asn Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Pro Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
                85                  90                  95

Leu Asn Gly Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu Gly
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 357 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double

(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..357

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

```
GAG GTG CAG CTG GTG GAG TCT GGG GGA GGC TTG GTA CAG CCT GGG GGG          48
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
  1               5                  10                  15

TCC CTG AGA CTC TCC TGC GCA GCC TCT GGA GTC TCC CTC AGT GGA TAC          96
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Val Ser Leu Ser Gly Tyr
             20                  25                  30

AAG ATG AAC TGG GTC CGC CAG GCT CCA GGG AAG GGG CTG GAA TGG GTC         144
Lys Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
         35                  40                  45

TCT TCC ATT ACT GGT ATG AGT AAT TAC ATA CAC TAC TCA GAC TCA GTG         192
Ser Ser Ile Thr Gly Met Ser Asn Tyr Ile His Tyr Ser Asp Ser Val
     50                  55                  60

AAG GGC CGA TTC ACC ATC TCC AGA GAC AAC GCC ATG AAC TCA CTG TAT         240
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Met Asn Ser Leu Tyr
 65                  70                  75                  80

CTG CAA ATG AAC AGC CTG ACA GCC GAG GAC ACG GGT GTT TAT TAT TGT         288
Leu Gln Met Asn Ser Leu Thr Ala Glu Asp Thr Gly Val Tyr Tyr Cys
                 85                  90                  95

GCG ACA CAA CCG GGG GAG CTG GCG CCT TTT GAC CAT TGG GGC CAG GGA         336
Ala Thr Gln Pro Gly Glu Leu Ala Pro Phe Asp His Trp Gly Gln Gly
            100                 105                 110

ACC CTG GTC ACC GTC TCC TCA                                            357
Thr Leu Val Thr Val Ser Ser
        115
```

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 119 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
  1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Val Ser Leu Ser Gly Tyr
             20                  25                  30

Lys Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
```

```
          35                  40                  45

Ser Ser Ile Thr Gly Met Ser Asn Tyr Ile His Tyr Ser Asp Ser Val
     50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Met Asn Ser Leu Tyr
 65                  70                  75                  80

Leu Gln Met Asn Ser Leu Thr Ala Glu Asp Thr Gly Val Tyr Tyr Cys
                 85                  90                  95

Ala Thr Gln Pro Gly Glu Leu Ala Pro Phe Asp His Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115
```

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 119 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Val Ser Leu Ser Gly Tyr
            20                  25                  30

Lys Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ser Ile Thr Gly Met Ser Asn Tyr Ile His Tyr Ser Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Met Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Thr Ala Glu Asp Thr Gly Val Tyr Tyr Cys
                85                  90                  95

Ala Thr Gln Pro Gly Glu Leu Ala Pro Phe Asp His Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115
```

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 98 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                  10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Glu Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Tyr Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg
```

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 138 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

```
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                  10                  15

Val His Ser Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln
            20                  25                  30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Val Ser Leu
        35                  40                  45

Ser Gly Tyr Lys Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ser Ser Ile Thr Gly Met Ser Asn Tyr Ile His Tyr Ser
65                  70                  75                  80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Met Asn
                85                  90                  95

Ser Leu Tyr Leu Gln Met Asn Ser Leu Thr Ala Glu Asp Thr Gly Val
```

100 105 110

Tyr Tyr Cys Ala Thr Gln Pro Gly Glu Leu Ala Pro Phe Asp His Trp
115 120 125

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
130 135

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 138 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15

Val His Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln
20 25 30

Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Val Ser Leu
35 40 45

Ser Gly Tyr Lys Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
50 55 60

Glu Trp Val Ser Ser Ile Thr Gly Met Ser Asn Tyr Ile His Tyr Ser
65 70 75 80

Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Met Asn
85 90 95

Ser Leu Tyr Leu Gln Met Asn Ser Leu Thr Ala Glu Asp Thr Gly Val
100 105 110

Tyr Tyr Cys Ala Thr Gln Pro Gly Glu Leu Ala Pro Phe Asp His Trp
115 120 125

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
130 135

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 111 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

```
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln
1               5                  10                  15

Lys Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Leu Gly Ala Gly
            20                  25                  30

Tyr Asp Val His Trp Tyr Arg Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Asp Asn Asn Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Pro Ser Ala Ser Leu Ala Ile Ser Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
                85                  90                  95

Leu Asn Gly Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu
            100                 105                 110
```

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 90 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                  10                  15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly
            20                  25                  30

Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
        35                  40                  45

Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65                  70                  75                  80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys
                85                  90
```

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 128 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

```
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                  10                  15

Val His Ser Glu Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly
            20                  25                  30

Gln Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile Gly Ala
        35                  40                  45

Gly Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys
    50                  55                  60

Leu Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val Pro Asp Arg
65                  70                  75                  80

Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly
                85                  90                  95

Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser
            100                 105                 110

Ser Leu Asn Gly Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr Val Leu
        115                 120                 125
```

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 130 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

```
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                  10                  15

Val His Ser Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala
            20                  25                  30

Pro Gly Gln Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Ile
        35                  40                  45

Gly Ala Gly Tyr Asp Val His Trp Tyr Gln Gln Leu Pro Gly Thr Ala
    50                  55                  60

Pro Lys Leu Leu Ile Tyr Gly Asn Ser Asn Arg Pro Ser Gly Val Pro
65                  70                  75                  80
```

Asp Arg Phe Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile
85 90 95

Thr Gly Leu Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr
100 105 110

Asp Ser Ser Leu Asn Gly Tyr Val Phe Gly Thr Gly Thr Gln Leu Thr
115 120 125

Val Leu
130

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6281 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GACGTCGCGG CCGCTCTAGG CCTCCAAAAA AGCCTCCTCA CTACTTCTGG AATAGCTCAG 60

AGGCCGAGGC GGCCTCGGCC TCTGCATAAA TAAAAAAAAT TAGTCAGCCA TGCATGGGGC 120

GGAGAATGGG CGGAACTGGG CGGAGTTAGG GGCGGGATGG GCGGAGTTAG GGGCGGGACT 180

ATGGTTGCTG ACTAATTGAG ATGCATGCTT TGCATACTTC TGCCTGCTGG GGAGCCTGGG 240

GACTTTCCAC ACCTGGTTGC TGACTAATTG AGATGCATGC TTTGCATACT TCTGCCTGCT 300

GGGGAGCCTG GGGACTTTCC ACACCCTAAC TGACACACAT TCCACAGAAT TAATTCCCGG 360

GGATCGATCC GTCGACGTAC GACTAGTTAT TAATAGTAAT CAATTACGGG GTCATTAGTT 420

CATAGCCCAT ATATGGAGTT CCGCGTTACA TAACTTACGG TAAATGGCCC GCCTGGCTGA 480

CCGCCCAACG ACCCCCGCCC ATTGACGTCA ATAATGACGT ATGTTCCCAT AGTAACGCCA 540

ATAGGGACTT TCCATTGACG TCAATGGGTG GACTATTTAC GGTAAACTGC CCACTTGGCA 600

GTACATCAAG TGTATCATAT GCCAAGTACG CCCCCTATTG ACGTCAATGA CGGTAAATGG 660

CCCGCCTGGC ATTATGCCCA GTACATGACC TTATGGGACT TTCCTACTTG GCAGTACATC 720

TACGTATTAG TCATCGCTAT TACCATGGTG ATGCGGTTTT GGCAGTACAT CAATGGGCGT 780

GGATAGCGGT TTGACTCACG GGGATTTCCA AGTCTCCACC CCATTGACGT CAATGGGAGT 840

TTGTTTTGGC ACCAAAATCA ACGGGACTTT CCAAAATGTC GTAACAACTC CGCCCCATTG 900

ACGCAAATGG GCGGTAGGCG TGTACGGTGG GAGGTCTATA TAAGCAGAGC TGGGTACGTG 960

AACCGTCAGA TCGCCTGGAG ACGCCATCGA ATTCTGAGCA CACAGGACCT CACCATGGGA 1020

TGGAGCTGTA TCATCCTCTT CTTGGTAGCA ACAGCTACAG GTGTCCACTC CGAGGTCCAA 1080

CTGCTCGAGT CTGGGGGAGG CTTGGTACAG CCTGGGGGGT CCCTGAGACT CTCCTGCGCA 1140

GCCTCTGGAG TCTCCCTCAG TGGATACAAG ATGAACTGGG TCCGCCAGGC TCCAGGGAAG 1200

GGGCTGGAAT GGGTCTCTTC CATTACTGGT ATGAGTAATT ACATACACTA CTCAGACTCA 1260

GTGAAGGGCC GATTCACCAT CTCCAGAGAC AACGCCATGA ACTCACTGTA TCTGCAAATG 1320

AACAGCCTGA CAGCCGAGGA CACGGGTGTT TATTATTGTG CGACACAACC GGGGGAGCTG 1380

GCGCCTTTTG ACCATTGGGG CCAGGGAACC CTGGTCACCG TCTCCTCAGC CTCCACCAAG 1440

GGCCCATCGG TCTTCCCCCT GGCACCCTCC TCCAAGAGCA CCTCTGGGGG CACAGCGGCC 1500

CTGGGCTGCC TGGTCAAGGA CTACTTCCCC GAACCGGTGA CGGTGTCGTG GAACTCAGGC 1560

GCCCTGACCA GCGGCGTGCA CACCTTCCCG GCTGTCCTAC AGTCCTCAGG ACTCTACTCC 1620

CTCAGCAGCG TGGTGACCGT GCCCTCCAGC AGCTTGGGCA CCCAGACCTA CATCTGCAAC 1680

GTGAATCACA AGCCCAGCAA CACCAAGGTG GACAAGAAAG TTGAGCCCAA ATCTTGTGAC 1740

AAAACTCACA CATGCCCACC GTGCCCAGCA CCTGAACTCC TGGGGGGACC GTCAGTCTTC 1800

CTCTTCCCCC CAAAACCCAA GGACACCCTC ATGATCTCCC GGACCCCTGA GGTCACATGC 1860

GTGGTGGTGG ACGTGAGCCA CGAAGACCCT GAGGTCAAGT TCAACTGGTA CGTGGACGGC 1920

GTGGAGGTGC ATAATGCCAA GACAAAGCCG CGGGAGGAGC AGTACAACAG CACGTACCGG 1980

GTGGTCAGCG TCCTCACCGT CCTGCACCAG GACTGGCTGA ATGGCAAGGA GTACAAGTGC 2040

AAGGTCTCCA ACAAAGCCCT CCCAGCCCCC ATCGAGAAAA CCATCTCCAA AGCCAAAGGG 2100

CAGCCCCGAG AACCACAGGT GTACACCCTG CCCCCATCCC GGGATGAGCT GACCAAGAAC 2160

CAGGTCAGCC TGACCTGCCT GGTCAAAGGC TTCTATCCCA GCGACATCGC CGTGGAGTGG 2220

GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC 2280

GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA GCAGGTGGCA GCAGGGGAAC 2340

GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC 2400

TCCCTGTCTC CGGGTAAATG ATAGATATCT ACGTATGATC AGCCTCGACT GTGCCTTCTA 2460

GTTGCCAGCC ATCTGTTGTT TGCCCCTCCC CCGTGCCTTC CTTGACCCTG GAAGGTGCCA 2520

CTCCCACTGT CCTTTCCTAA TAAAATGAGG AAATTGCATC GCATTGTCTG AGTAGGTGTC 2580

ATTCTATTCT GGGGGGTGGG GTGGGGCAGG ACAGCAAGGG GGAGGATTGG GAAGACAATA 2640

GCAGGCATGC TGGGGATGCG GTGGGCTCTA TGGAACCAGC TGGGGCTCGA CAGCGCTGGA 2700

TCTCCCGATC CCCAGCTTTG CTTCTCAATT TCTTATTTGC ATAATGAGAA AAAAAGGAAA 2760

ATTAATTTTA ACACCAATTC AGTAGTTGAT TGAGCAAATG CGTTGCCAAA AAGGATGCTT 2820

TAGAGACAGT GTTCTCTGCA CAGATAAGGA CAAACATTAT TCAGAGGGAG TACCCAGAGC 2880

TGAGACTCCT AAGCCAGTGA GTGGCACAGC ATTCTAGGGA GAAATATGCT TGTCATCACC 2940

GAAGCCTGAT TCCGTAGAGC CACACCTTGG TAAGGGCCAA TCTGCTCACA CAGGATAGAG 3000

AGGGCAGGAG CCAGGGCAGA GCATATAAGG TGAGGTAGGA TCAGTTGCTC CTCACATTTG 3060

CTTCTGACAT AGTTGTGTTG GGAGCTTGGA TAGCTTGGAC AGCTCAGGGC TGCGATTTCG 3120

CGCCAAACTT GACGGCAATC CTAGCGTGAA GGCTGGTAGG ATTTTATCCC CGCTGCCATC 3180

ATGGTTCGAC CATTGAACTG CATCGTCGCC GTGTCCCAAA ATATGGGGAT TGGCAAGAAC 3240

GGAGACCTAC CCTGGCCTCC GCTCAGGAAC GAGTTCAAGT ACTTCCAAAG AATGACCACA 3300

ACCTCTTCAG TGGAAGGTAA ACAGAATCTG GTGATTATGG GTAGGAAAAC CTGGTTCTCC 3360

ATTCCTGAGA AGAATCGACC TTTAAAGGAC AGAATTAATA TAGTTCTCAG TAGAGAACTC 3420

AAAGAACCAC CACGAGGAGC TCATTTTCTT GCCAAAAGTT TGGATGATGC CTTAAGACTT 3480

ATTGAACAAC CGGAATTGGC AAGTAAAGTA GACATGGTTT GGATAGTCGG AGGCAGTTCT 3540

GTTTACCAGG AAGCCATGAA TCAACCAGGC CACCTTAGAC TCTTTGTGAC AAGGATCATG 3600

CAGGAATTTG AAAGTGACAC GTTTTTCCCA GAAATTGATT TGGGGAAATA TAAACTTCTC 3660

CCAGAATACC CAGGCGTCCT CTCTGAGGTC CAGGAGGAAA AAGGCATCAA GTATAAGTTT 3720

GAAGTCTACG AGAAGAAAGA CTAACAGGAA GATGCTTTCA AGTTCTCTGC TCCCCTCCTA 3780

AAGCTATGCA TTTTTATAAG ACCATGGGAC TTTTGCTGGC TTTAGATCAG CCTCGACTGT 3840

GCCTTCTAGT TGCCAGCCAT CTGTTGTTTG CCCCTCCCCC GTGCCTTCCT TGACCCTGGA 3900

AGGTGCCACT CCCACTGTCC TTTCCTAATA AAATGAGGAA ATTGCATCGC ATTGTCTGAG 3960

TAGGTGTCAT TCTATTCTGG GGGGTGGGGT GGGGCAGGAC AGCAAGGGGG AGGATTGGGA 4020

AGACAATAGC AGGCATGCTG GGGATGCGGT GGGCTCTATG GAACCAGCTG GGGCTCGATC 4080

GAGTGTATGA CTGCGGCCGC GATCCCGTCG AGAGCTTGGC GTAATCATGG TCATAGCTGT 4140

TTCCTGTGTG AAATTGTTAT CCGCTCACAA TTCCACACAA CATACGAGCC GGAAGCATAA 4200

AGTGTAAAGC CTGGGGTGCC TAATGAGTGA GCTAACTCAC ATTAATTGCG TTGCGCTCAC 4260

TGCCCGCTTT CCAGTCGGGA AACCTGTCGT GCCAGCTGCA TTAATGAATC GGCCAACGCG 4320

CGGGGAGAGG CGGTTTGCGT ATTGGGCGCT CTTCCGCTTC CTCGCTCACT GACTCGCTGC 4380

GCTCGGTCGT TCGGCTGCGG CGAGCGGTAT CAGCTCACTC AAAGGCGGTA ATACGGTTAT 4440

CCACAGAATC AGGGGATAAC GCAGGAAAGA ACATGTGAGC AAAAGGCCAG CAAAAGGCCA 4500

GGAACCGTAA AAAGGCCGCG TTGCTGGCGT TTTTCCATAG GCTCCGCCCC CCTGACGAGC 4560

ATCACAAAAA TCGACGCTCA AGTCAGAGGT GGCGAAACCC GACAGGACTA TAAAGATACC 4620

AGGCGTTTCC CCCTGGAAGC TCCCTCGTGC GCTCTCCTGT TCCGACCCTG CCGCTTACCG 4680

GATACCTGTC CGCCTTTCTC CCTTCGGGAA GCGTGGCGCT TTCTCAATGC TCACGCTGTA 4740

GGTATCTCAG TTCGGTGTAG GTCGTTCGCT CCAAGCTGGG CTGTGTGCAC GAACCCCCCG 4800

TTCAGCCCGA CCGCTGCGCC TTATCCGGTA ACTATCGTCT TGAGTCCAAC CCGGTAAGAC 4860

```
ACGACTTATC GCCACTGGCA GCAGCCACTG GTAACAGGAT TAGCAGAGCG AGGTATGTAG    4920

GCGGTGCTAC AGAGTTCTTG AAGTGGTGGC CTAACTACGG CTACACTAGA AGGACAGTAT    4980

TTGGTATCTG CGCTCTGCTG AAGCCAGTTA CCTTCGGAAA AAGAGTTGGT AGCTCTTGAT    5040

CCGGCAAACA AACCACCGCT GGTAGCGGTG GTTTTTTTGT TTGCAAGCAG CAGATTACGC    5100

GCAGAAAAAA AGGATCTCAA GAAGATCCTT TGATCTTTTC TACGGGGTCT GACGCTCAGT    5160

GGAACGAAAA CTCACGTTAA GGGATTTTGG TCATGAGATT ATCAAAAAGG ATCTTCACCT    5220

AGATCCTTTT AAATTAAAAA TGAAGTTTTA AATCAATCTA AAGTATATAT GAGTAAACTT    5280

GGTCTGACAG TTACCAATGC TTAATCAGTG AGGCACCTAT CTCAGCGATC TGTCTATTTC    5340

GTTCATCCAT AGTTGCCTGA CTCCCCGTCG TGTAGATAAC TACGATACGG GAGGGCTTAC    5400

CATCTGGCCC CAGTGCTGCA ATGATACCGC GAGACCCACG CTCACCGGCT CCAGATTTAT    5460

CAGCAATAAA CCAGCCAGCC GGAAGGGCCG AGCGCAGAAG TGGTCCTGCA ACTTTATCCG    5520

CCTCCATCCA GTCTATTAAT TGTTGCCGGG AAGCTAGAGT AAGTAGTTCG CCAGTTAATA    5580

GTTTGCGCAA CGTTGTTGCC ATTGCTACAG GCATCGTGGT GTCACGCTCG TCGTTTGGTA    5640

TGGCTTCATT CAGCTCCGGT TCCCAACGAT CAAGGCGAGT TACATGATCC CCCATGTTGT    5700

GCAAAAAAGC GGTTAGCTCC TTCGGTCCTC CGATCGTTGT CAGAAGTAAG TTGGCCGCAG    5760

TGTTATCACT CATGGTTATG GCAGCACTGC ATAATTCTCT TACTGTCATG CCATCCGTAA    5820

GATGCTTTTC TGTGACTGGT GAGTACTCAA CCAAGTCATT CTGAGAATAG TGTATGCGGC    5880

GACCGAGTTG CTCTTGCCCG GCGTCAATAC GGGATAATAC CGCGCCACAT AGCAGAACTT    5940

TAAAAGTGCT CATCATTGGA AAACGTTCTT CGGGGCGAAA ACTCTCAAGG ATCTTACCGC    6000

TGTTGAGATC CAGTTCGATG TAACCCACTC GTGCACCCAA CTGATCTTCA GCATCTTTTA    6060

CTTTCACCAG CGTTTCTGGG TGAGCAAAAA CAGGAAGGCA AAATGCCGCA AAAAAGGGAA    6120

TAAGGGCGAC ACGGAAATGT TGAATACTCA TACTCTTCCT TTTTCAATAT TATTGAAGCA    6180

TTTATCAGGG TTATTGTCTC ATGAGCGGAT ACATATTTGA ATGTATTTAG AAAAATAAAC    6240

AAATAGGGGT TCCGCGCACA TTTCCCCGAA AAGTGCCACC T                        6281
```

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5679 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

GACGTCGCGG CCGCTCTAGG CCTCCAAAAA AGCCTCCTCA CTACTTCTGG AATAGCTCAG 60

AGGCCGAGGC GGCCTCGGCC TCTGCATAAA TAAAAAAAAT TAGTCAGCCA TGCATGGGGC 120

GGAGAATGGG CGGAACTGGG CGGAGTTAGG GGCGGGATGG GCGGAGTTAG GGGCGGGACT 180

ATGGTTGCTG ACTAATTGAG ATGCATGCTT TGCATACTTC TGCCTGCTGG GGAGCCTGGG 240

GACTTTCCAC ACCTGGTTGC TGACTAATTG AGATGCATGC TTTGCATACT TCTGCCTGCT 300

GGGGAGCCTG GGGACTTTCC ACACCCTAAC TGACACACAT TCCACAGAAT TAATTCCCGG 360

GGATCGATCC GTCGACGTAC GACTAGTTAT TAATAGTAAT CAATTACGGG GTCATTAGTT 420

CATAGCCCAT ATATGGAGTT CCGCGTTACA TAACTTACGG TAAATGGCCC GCCTGGCTGA 480

CCGCCCAACG ACCCCCGCCC ATTGACGTCA ATAATGACGT ATGTTCCCAT AGTAACGCCA 540

ATAGGGACTT TCCATTGACG TCAATGGGTG GACTATTTAC GGTAAACTGC CCACTTGGCA 600

GTACATCAAG TGTATCATAT GCCAAGTACG CCCCCTATTG ACGTCAATGA CGGTAAATGG 660

CCCGCCTGGC ATTATGCCCA GTACATGACC TTATGGGACT TTCCTACTTG GCAGTACATC 720

TACGTATTAG TCATCGCTAT TACCATGGTG ATGCGGTTTT GGCAGTACAT CAATGGGCGT 780

GGATAGCGGT TTGACTCACG GGGATTTCCA AGTCTCCACC CCATTGACGT CAATGGGAGT 840

TTGTTTTGGC ACCAAAATCA ACGGGACTTT CCAAAATGTC GTAACAACTC CGCCCCATTG 900

ACGCAAATGG GCGGTAGGCG TGTACGGTGG GAGGTCTATA TAAGCAGAGC TGGGTACGTG 960

AACCGTCAGA TCGCCTGGAG ACGCCATCGA ATTCTGAGCA CACAGGACCT CACCATGGGA 1020

TGGAGCTGTA TCATCCTCTT CTTGGTAGCA ACAGCTACAG GTGTCCACTC CGAGCTCACG 1080

CAGCCGCCCT CAGTCTCTGC GGCCCCAGGA CAGAAGGTCA CCATCTCCTG CACTGGGAGC 1140

AGCTCCAACC TCGGGGCAGG TTATGATGTT CACTGGTACC GGCAACTTCC AGGGACAGCC 1200

CCCAAACTCC TCATCTATGA TAACAACAAT CGGCCCTCAG GGGTCCCTGA CCGATTCTCT 1260

GGCTCCAAGT CTGGCCCCTC AGCCTCCCTG GCCATCTCTG GGCTCCAGGC TGAGGATGAG 1320

GCTGATTATT ACTGCCAGTC CTATGACAGC AGCCTGAATG GTTATGTCTT CGGAACTGGG 1380

ACCCAGCTCA CCGTCCTAGG TCAGCCCAAG GCTGCCCCCT CGGTCACTCT GTTCCCGCCC 1440

TCCTCTGAGG AGCTTCAAGC CAACAAGGCC ACACTGGTGT GTCTCATAAG TGACTTCTAC 1500

CCGGGAGCCG TGACAGTGGC CTGGAAGGCA ATTAGCAGCC CCGTCAAGGC GGGAGTGGAG 1560

ACCACCACAC CCTCCAAACA AAGCAACAAC AAGTACGCGG CCAGCAGCTA TCTGAGCCTG 1620

ACGCCTGAGC AGTGGAAGTC CCACAGAAGG TACAGCTGCC AGGTCACGCA TGAAGGGAGC 1680

ACCGTGGAGA AGACAGTGGC CCCTACAGAA TGTTCATAGT TCTAGATCTA CGTATGATCA 1740

GCCTCGACTG TGCCTTCTAG TTGCCAGCCA TCTGTTGTTT GCCCCTCCCC CGTGCCTTCC 1800

TTGACCCTGG AAGGTGCCAC TCCCACTGTC CTTTCCTAAT AAAATGAGGA AATTGCATCG 1860

CATTGTCTGA GTAGGTGTCA TTCTATTCTG GGGGGTGGGG TGGGGCAGGA CAGCAAGGGG 1920

GAGGATTGGG AAGACAATAG CAGGCATGCT GGGGATGCGG TGGGCTCTAT GGAACCAGCT 1980

GGGGCTCGAC AGCTCGAGCT AGCTTTGCTT CTCAATTTCT TATTTGCATA ATGAGAAAAA 2040

AAGGAAAATT AATTTTAACA CCAATTCAGT AGTTGATTGA GCAAATGCGT TGCCAAAAAG 2100

GATGCTTTAG AGACAGTGTT CTCTGCACAG ATAAGGACAA ACATTATTCA GAGGGAGTAC 2160

CCAGAGCTGA GACTCCTAAG CCAGTGAGTG GCACAGCATT CTAGGGAGAA ATATGCTTGT 2220

CATCACCGAA GCCTGATTCC GTAGAGCCAC ACCTTGGTAA GGGCCAATCT GCTCACACAG 2280

GATAGAGAGG GCAGGAGCCA GGGCAGAGCA TATAAGGTGA GGTAGGATCA GTTGCTCCTC 2340

ACATTTGCTT CTGACATAGT TGTGTTGGGA GCTTGGATCG ATCCACCATG GTTGAACAAG 2400

ATGGATTGCA CGCAGGTTCT CCGGCCGCTT GGGTGGAGAG GCTATTCGGC TATGACTGGG 2460

CACAACAGAC AATCGGCTGC TCTGATGCCG CCGTGTTCCG GCTGTCAGCG CAGGGGCGCC 2520

CGGTTCTTTT TGTCAAGACC GACCTGTCCG GTGCCCTGAA TGAACTGCAG GACGAGGCAG 2580

CGCGGCTATC GTGGCTGGCC ACGACGGGCG TTCCTTGCGC AGCTGTGCTC GACGTTGTCA 2640

CTGAAGCGGG AAGGGACTGG CTGCTATTGG GCGAAGTGCC GGGGCAGGAT CTCCTGTCAT 2700

CTCACCTTGC TCCTGCCGAG AAAGTATCCA TCATGGCTGA TGCAATGCGG CGGCTGCATA 2760

CGCTTGATCC GGCTACCTGC CCATTCGACC ACCAAGCGAA ACATCGCATC GAGCGAGCAC 2820

GTACTCGGAT GGAAGCCGGT CTTGTCGATC AGGATGATCT GGACGAAGAG CATCAGGGGC 2880

TCGCGCCAGC CGAACTGTTC GCCAGGCTCA AGGCGCGCAT GCCCGACGGC GAGGATCTCG 2940

TCGTGACCCA TGGCGATGCC TGCTTGCCGA ATATCATGGT GGAAAATGGC CGCTTTTCTG 3000

GATTCATCGA CTGTGGCCGG CTGGGTGTGG CGGACCGCTA TCAGGACATA GCGTTGGCTA 3060

CCCGTGATAT TGCTGAAGAG CTTGGCGGCG AATGGGCTGA CCGCTTCCTC GTGCTTTACG 3120

GTATCGCCGC TCCCGATTCG CAGCGCATCG CCTTCTATCG CCTTCTTGAC GAGTTCTTCT 3180

GAGCGGGACT CTGGGGTTCG AAATGACCGA CCAAGCGACG CCCAACCTGC CATCACGAGA 3240

TTTCGATTCC ACCGCCGCCT TCTATGAAAG GTTGGGCTTC GGAATCGTTT TCCGGGACGC 3300

CGGCTGGATG ATCCTCCAGC GCGGGGATCT CATGCTGGAG TTCTTCGCCC ACCCCAACTT 3360

GTTTATTGCA GCTTATAATG GTTACAAATA AAGCAATAGC ATCACAAATT TCACAAATAA 3420

AGCATTTTTT TCACTGCATT CTAGTTGTGG TTTGTCCAAA CTCATCAATG TATCTTATCA 3480

TGTCTGGATC GCGGCCGCGA TCCCGTCGAG AGCTTGGCGT AATCATGGTC ATAGCTGTTT 3540

CCTGTGTGAA ATTGTTATCC GCTCACAATT CCACACAACA TACGAGCCGG AAGCATAAAG 3600

TGTAAAGCCT GGGGTGCCTA ATGAGTGAGC TAACTCACAT TAATTGCGTT GCGCTCACTG 3660

CCCGCTTTCC AGTCGGGAAA CCTGTCGTGC CAGCTGCATT AATGAATCGG CCAACGCGCG 3720

GGGAGAGGCG GTTTGCGTAT TGGGCGCTCT TCCGCTTCCT CGCTCACTGA CTCGCTGCGC 3780

TCGGTCGTTC GGCTGCGGCG AGCGGTATCA GCTCACTCAA AGGCGGTAAT ACGGTTATCC 3840

ACAGAATCAG GGGATAACGC AGGAAAGAAC ATGTGAGCAA AAGGCCAGCA AAAGGCCAGG 3900

AACCGTAAAA AGGCCGCGTT GCTGGCGTTT TTCCATAGGC TCCGCCCCCC TGACGAGCAT 3960

CACAAAAATC GACGCTCAAG TCAGAGGTGG CGAAACCCGA CAGGACTATA AAGATACCAG 4020

GCGTTTCCCC CTGGAAGCTC CCTCGTGCGC TCTCCTGTTC CGACCCTGCC GCTTACCGGA 4080

TACCTGTCCG CCTTTCTCCC TTCGGGAAGC GTGGCGCTTT CTCAATGCTC ACGCTGTAGG 4140

TATCTCAGTT CGGTGTAGGT CGTTCGCTCC AAGCTGGGCT GTGTGCACGA ACCCCCCGTT 4200

CAGCCCGACC GCTGCGCCTT ATCCGGTAAC TATCGTCTTG AGTCCAACCC GGTAAGACAC 4260

GACTTATCGC CACTGGCAGC AGCCACTGGT AACAGGATTA GCAGAGCGAG GTATGTAGGC 4320

GGTGCTACAG AGTTCTTGAA GTGGTGGCCT AACTACGGCT ACACTAGAAG GACAGTATTT 4380

GGTATCTGCG CTCTGCTGAA GCCAGTTACC TTCGGAAAAA GAGTTGGTAG CTCTTGATCC 4440

GGCAAACAAA CCACCGCTGG TAGCGGTGGT TTTTTTGTTT GCAAGCAGCA GATTACGCGC 4500

AGAAAAAAAG GATCTCAAGA AGATCCTTTG ATCTTTTCTA CGGGGTCTGA CGCTCAGTGG 4560

AACGAAAACT CACGTTAAGG GATTTTGGTC ATGAGATTAT CAAAAAGGAT CTTCACCTAG 4620

ATCCTTTTAA ATTAAAAATG AAGTTTTAAA TCAATCTAAA GTATATATGA GTAAACTTGG 4680

TCTGACAGTT ACCAATGCTT AATCAGTGAG GCACCTATCT CAGCGATCTG TCTATTTCGT 4740

TCATCCATAG TTGCCTGACT CCCCGTCGTG TAGATAACTA CGATACGGGA GGGCTTACCA 4800

TCTGGCCCCA GTGCTGCAAT GATACCGCGA GACCCACGCT CACCGGCTCC AGATTTATCA 4860

GCAATAAACC AGCCAGCCGG AAGGGCCGAG CGCAGAAGTG GTCCTGCAAC TTTATCCGCC 4920

TCCATCCAGT CTATTAATTG TTGCCGGGAA GCTAGAGTAA GTAGTTCGCC AGTTAATAGT 4980

TTGCGCAACG TTGTTGCCAT TGCTACAGGC ATCGTGGTGT CACGCTCGTC GTTTGGTATG 5040

GCTTCATTCA GCTCCGGTTC CCAACGATCA AGGCGAGTTA CATGATCCCC CATGTTGTGC 5100

AAAAAAGCGG TTAGCTCCTT CGGTCCTCCG ATCGTTGTCA GAAGTAAGTT GGCCGCAGTG 5160

TTATCACTCA TGGTTATGGC AGCACTGCAT AATTCTCTTA CTGTCATGCC ATCCGTAAGA 5220

TGCTTTTCTG TGACTGGTGA GTACTCAACC AAGTCATTCT GAGAATAGTG TATGCGGCGA 5280

CCGAGTTGCT CTTGCCCGGC GTCAATACGG GATAATACCG CGCCACATAG CAGAACTTTA 5340

AAAGTGCTCA TCATTGGAAA ACGTTCTTCG GGGCGAAAAC TCTCAAGGAT CTTACCGCTG 5400

TTGAGATCCA GTTCGATGTA ACCCACTCGT GCACCCAACT GATCTTCAGC ATCTTTTACT 5460

TTCACCAGCG TTTCTGGGTG AGCAAAAACA GGAAGGCAAA ATGCCGCAAA AAAGGGAATA 5520

AGGGCGACAC GGAAATGTTG AATACTCATA CTCTTCCTTT TTCAATATTA TTGAAGCATT 5580

TATCAGGGTT ATTGTCTCAT GAGCGGATAC ATATTTGAAT GTATTTAGAA AAATAAACAA 5640

ATAGGGGTTC CGCGCACATT TCCCCGAAAA GTGCCACCT 5679

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1442 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GAATTCTGAG CACACAGGAC CTCACCATGG GATGGAGCTG TATCATCCTC TTCTTGGTAG 60

CAACAGCTAC AGGTGTCCAC TCCGAGGTGC AGCTGGTGGA GTCTGGGGGA GGCTTGGTAC 120

AGCCTGGGGG GTCCCTGAGA CTCTCCTGCG CAGCCTCTGG AGTCTCCCTC AGTGGATACA 180

AGATGAACTG GGTCCGCCAG GCTCCAGGGA AGGGGCTGGA ATGGGTCTCT TCCATTACTG 240

GTATGAGTAA TTACATACAC TACTCAGACT CAGTGAAGGG CCGATTCACC ATCTCCAGAG 300

ACAACGCCAT GAACTCACTG TATCTGCAAA TGAACAGCCT GACAGCCGAG GACACGGGTG 360

TTTATTATTG TGCGACACAA CCGGGGGAGC TGGCGCCTTT TGACCATTGG GGCCAGGGAA 420

CCCTGGTCAC CGTCTCCTCA GCCTCCACCA AGGGCCCATC GGTCTTCCCC CTGGCACCCT 480

CCTCCAAGAG CACCTCTGGG GGCACAGCGG CCCTGGGCTG CCTGGTCAAG GACTACTTCC 540

CCGAACCGGT GACGGTGTCG TGGAACTCAG GCGCCCTGAC CAGCGGCGTG CACACCTTCC 600

CGGCTGTCCT ACAGTCCTCA GGACTCTACT CCCTCAGCAG CGTGGTGACC GTGCCCTCCA 660

GCAGCTTGGG CACCCAGACC TACATCTGCA ACGTGAATCA CAAGCCCAGC AACACCAAGG 720

TGGACAAGAA AGTTGAGCCC AAATCTTGTG ACAAAACTCA CACATGCCCA CCGTGCCCAG 780

CACCTGAACT CCTGGGGGGA CCGTCAGTCT TCCTCTTCCC CCCAAAACCC AAGGACACCC 840

TCATGATCTC CCGGACCCCT GAGGTCACAT GCGTGGTGGT GGACGTGAGC CACGAAGACC 900

CTGAGGTCAA GTTCAACTGG TACGTGGACG GCGTGGAGGT GCATAATGCC AAGACAAAGC 960

CGCGGGAGGA GCAGTACAAC AGCACGTACC GGGTGGTCAG CGTCCTCACC GTCCTGCACC 1020

AGGACTGGCT GAATGGCAAG GAGTACAAGT GCAAGGTCTC CAACAAAGCC CTCCCAGCCC 1080

CCATCGAGAA AACCATCTCC AAAGCCAAAG GGCAGCCCCG AGAACCACAG GTGTACACCC 1140

TGCCCCCATC CCGGGATGAG CTGACCAAGA ACCAGGTCAG CCTGACCTGC CTGGTCAAAG 1200

GCTTCTATCC CAGCGACATC GCCGTGGAGT GGGAGAGCAA TGGGCAGCCG GAGAACAACT 1260

ACAAGACCAC GCCTCCCGTG CTGGACTCCG ACGGCTCCTT CTTCCTCTAC AGCAAGCTCA 1320

CCGTGGACAA GAGCAGGTGG CAGCAGGGGA ACGTCTTCTC ATGCTCCGTG ATGCATGAGG 1380

CTCTGCACAA CCACTACACG CAGAAGAGCC TCTCCCTGTC TCCGGGTAAA TGATAGATAT 1440

CT 1442

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 762 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

GAATTCTGAG CACACAGGAC CTCACCATGG GATGGAGCTG TATCATCCTC TTCTTGGTAG 60

CAACAGCTAC AGGTGTCCAC TCCCAGTCTG TGTTGACGCA GCCGCCCTCA GTCTCTGCGG 120

CCCCAGGACA GAAGGTCACC ATCTCCTGCA CTGGGAGCAG CTCCAACCTC GGGGCAGGTT 180

ATGATGTTCA CTGGTACCGG CAACTTCCAG GGACAGCCCC CAAACTCCTC ATCTATGATA 240

ACAACAATCG GCCCTCAGGG GTCCCTGACC GATTCTCTGG CTCCAAGTCT GGCCCCTCAG 300

CCTCCCTGGC CATCTCTGGG CTCCAGGCTG AGGATGAGGC TGATTATTAC TGCCAGTCCT 360

ATGACAGCAG CCTGAATGGT TATGTCTTCG GAACTGGGAC CCAGCTCACC GTCCTAGGTC 420

AGCCCAAGGC TGCCCCCTCG GTCACTCTGT TCCCGCCCTC CTCTGAGGAG CTTCAAGCCA 480

ACAAGGCCAC ACTGGTGTGT CTCATAAGTG ACTTCTACCC GGGAGCCGTG ACAGTGGCCT 540

GGAAGGCAAT TAGCAGCCCC GTCAAGGCGG GAGTGGAGAC CACCACACCC TCCAAACAAA 600

GCAACAACAA GTACGCGGCC AGCAGCTATC TGAGCCTGAC GCCTGAGCAG TGGAAGTCCC 660

ACAGAAGGTA CAGCTGCCAG GTCACGCATG AAGGGAGCAC CGTGGAGAAG ACAGTGGCCC 720

CTACAGAATG TTCATAGTTC TAGATCTACG TATGATCAGC CT 762

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Glu Val Gln Leu Leu Glu
1 5

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Glu Val Gln Leu Val Glu
1 5

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1899 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 14..1735

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

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GGGGCAAATA ACA ATG GAG TTG CTA ATC CTC AAA GCA AAT GCA ATT ACC          49
               Met Glu Leu Leu Ile Leu Lys Ala Asn Ala Ile Thr
                 1               5                  10

ACA ATC CTC ACT GCA GTC ACA TTT TGT TTT GCT TCT GGT CAA AAC ATC         97
Thr Ile Leu Thr Ala Val Thr Phe Cys Phe Ala Ser Gly Gln Asn Ile
        15                  20                  25

ACT GAA GAA TTT TAT CAA TCA ACA TGC AGT GCA GTT AGC AAA GGC TAT        145
Thr Glu Glu Phe Tyr Gln Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr
    30                  35                  40

CTT AGT GCT CTG AGA ACT GGT TGG TAT ACC AGT GTT ATA ACT ATA GAA        193
Leu Ser Ala Leu Arg Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu
45                  50                  55                  60

TTA AGT AAT ATC AAG GAA AAT AAG TGT AAT GGA ACA GAT GCT AAG GTA        241
Leu Ser Asn Ile Lys Glu Asn Lys Cys Asn Gly Thr Asp Ala Lys Val
                65                  70                  75

AAA TTG ATA AAA CAA GAA TTA GAT AAA TAT AAA AAT GCT GTA ACA GAA        289
Lys Leu Ile Lys Gln Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu
            80                  85                  90

TTG CAG TTG CTC ATG CAA AGC ACA CCA CCA ACA AAC AAT CGA GCC AGA        337
Leu Gln Leu Leu Met Gln Ser Thr Pro Pro Thr Asn Asn Arg Ala Arg
        95                  100                 105
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AGA GAA CTA CCA AGG TTT ATG AAT TAT ACA CTC AAC AAT GCC AAA AAA        385
Arg Glu Leu Pro Arg Phe Met Asn Tyr Thr Leu Asn Asn Ala Lys Lys
    110                 115                 120

ACC AAT GTA ACA TTA AGC AAG AAA AGG AAA AGA AGA TTT CTT GGT TTT        433
Thr Asn Val Thr Leu Ser Lys Lys Arg Lys Arg Arg Phe Leu Gly Phe
125                 130                 135                 140

TTG TTA GGT GTT GGA TCT GCA ATC GCC AGT GGC GTT GCT GTA TCT AAG        481
Leu Leu Gly Val Gly Ser Ala Ile Ala Ser Gly Val Ala Val Ser Lys
                145                 150                 155

GTC CTG CAC CTA GAA GGG GAA GTG AAC AAG ATC AAA AGT GCT CTA CTA        529
Val Leu His Leu Glu Gly Glu Val Asn Lys Ile Lys Ser Ala Leu Leu
            160                 165                 170

TCC ACA AAC AAG GCT GTA GTC AGC TTA TCA AAT GGA GTT AGT GTC TTA        577
Ser Thr Asn Lys Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu
        175                 180                 185

ACC AGC AAA GTG TTA GAC CTC AAA AAC TAT ATA GAT AAA CAA TTG TTA        625
Thr Ser Lys Val Leu Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu
    190                 195                 200

CCT ATT GTG AAC AAG CAA AGC TGC AGC ATA TCA AAT ATA GAA ACT GTG        673
Pro Ile Val Asn Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val
205                 210                 215                 220

ATA GAG TTC CAA CAA AAG AAC AAC AGA CTA CTA GAG ATT ACC AGG GAA        721
Ile Glu Phe Gln Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu
                225                 230                 235

TTT AGT GTT AAT GCA GGT GTA ACT ACA CCT GTA AGC ACT TAC ATG TTA        769
Phe Ser Val Asn Ala Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu
            240                 245                 250

ACT AAT AGT GAA TTA TTG TCA TTA ATC AAT GAT ATG CCT ATA ACA AAT        817
Thr Asn Ser Glu Leu Leu Ser Leu Ile Asn Asp Met Pro Ile Thr Asn
        255                 260                 265

GAT CAG AAA AAG TTA ATG TCC AAC AAT GTT CAA ATA GTT AGA CAG CAA        865
Asp Gln Lys Lys Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln
    270                 275                 280

AGT TAC TCT ATC ATG TCC ATA ATA AAA GAG GAA GTC TTA GCA TAT GTA        913
Ser Tyr Ser Ile Met Ser Ile Ile Lys Glu Glu Val Leu Ala Tyr Val
285                 290                 295                 300

GTA CAA TTA CCA CTA TAT GGT GTT ATA GAT ACA CCC TGT TGG AAA CTA        961
Val Gln Leu Pro Leu Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys Leu
                305                 310                 315

CAC ACA TCC CCT CTA TGT ACA ACC AAC ACA AAA GAA GGG TCC AAC ATC       1009
His Thr Ser Pro Leu Cys Thr Thr Asn Thr Lys Glu Gly Ser Asn Ile
            320                 325                 330

TGT TTA ACA AGA ACT GAC AGA GGA TGG TAC TGT GAC AAT GCA GGA TCA       1057
Cys Leu Thr Arg Thr Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser
        335                 340                 345

GTA TCT TTC TTC CCA CAA GCT GAA ACA TGT AAA GTT CAA TCA AAT CGA       1105
Val Ser Phe Phe Pro Gln Ala Glu Thr Cys Lys Val Gln Ser Asn Arg
    350                 355                 360
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GTA TTT TGT GAC ACA ATG AAC AGT TTA ACA TTA CCA AGT GAA ATA AAT      1153
Val Phe Cys Asp Thr Met Asn Ser Leu Thr Leu Pro Ser Glu Ile Asn
365                 370                 375                 380

CTC TGC AAT GTT GAC ATA TTC AAC CCC AAA TAT GAT TGT AAA ATT ATG      1201
Leu Cys Asn Val Asp Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met
                385                 390                 395

ACT TCA AAA ACA GAT GTA AGC AGC TCC GTT ATC ACA TCT CTA GGA GCC      1249
Thr Ser Lys Thr Asp Val Ser Ser Ser Val Ile Thr Ser Leu Gly Ala
            400                 405                 410

ATT GTG TCA TGC TAT GGC AAA ACT AAA TGT ACA GCA TCC AAT AAA AAT      1297
Ile Val Ser Cys Tyr Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn
        415                 420                 425

CGT GGA ATC ATA AAG ACA TTT TCT AAC GGG TGC GAT TAT GTA TCA AAT      1345
Arg Gly Ile Ile Lys Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn
    430                 435                 440

AAA GGG ATG GAC ACT GTG TCT GTA GGT AAC ACA TTA TAT TAT GTA AAT      1393
Lys Gly Met Asp Thr Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn
445                 450                 455                 460

AAG CAA GAA GGT AAA AGT CTC TAT GTA AAA GGT GAA CCA ATA ATA AAT      1441
Lys Gln Glu Gly Lys Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile Asn
                465                 470                 475

TTC TAT GAC CCA TTA GTA TTC CCC TCT GAT GAA TTT GAT GCA TCA ATA      1489
Phe Tyr Asp Pro Leu Val Phe Pro Ser Asp Glu Phe Asp Ala Ser Ile
            480                 485                 490

TCT CAA GTC AAC GAG AAG ATT AAC CAG AGC CTA GCA TTT ATT CGT AAA      1537
Ser Gln Val Asn Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys
        495                 500                 505

TCC GAT GAA TTA TTA CAT AAT GTA AAT GCT GGT AAA TCC ACC ACA AAT      1585
Ser Asp Glu Leu Leu His Asn Val Asn Ala Gly Lys Ser Thr Thr Asn
    510                 515                 520

ATC ATG ATA ACT ACT ATA ATT ATA GTG ATT ATA GTA ATA TTG TTA TCA      1633
Ile Met Ile Thr Thr Ile Ile Ile Val Ile Ile Val Ile Leu Leu Ser
525                 530                 535                 540

TTA ATT GCT GTT GGA CTG CTC TTA TAC TGT AAG GCC AGA AGC ACA CCA      1681
Leu Ile Ala Val Gly Leu Leu Leu Tyr Cys Lys Ala Arg Ser Thr Pro
                545                 550                 555

GTC ACA CTA AGC AAA GAT CAA CTG AGT GGT ATA AAT AAT ATT GCA TTT      1729
Val Thr Leu Ser Lys Asp Gln Leu Ser Gly Ile Asn Asn Ile Ala Phe
            560                 565                 570

AGT AAC TAAATAAAAA TAGCACCTAA TCATGTTCTT ACAATGGTTT ACTATCTGCT      1785
Ser Asn

CATAGACAAC CCATCTGTCA TTGGATTTTC TTAAAATCTG AACTTCATCG AAACTCTCAT   1845

CTATAAACCA TCTCACTTAC ACTATTTAAG TAGATTCCTA GTTTATAGTT ATAT         1899
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(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 574 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

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Met Glu Leu Leu Ile Leu Lys Ala Asn Ala Ile Thr Thr Ile Leu Thr
 1               5                  10                  15

Ala Val Thr Phe Cys Phe Ala Ser Gly Gln Asn Ile Thr Glu Glu Phe
            20                  25                  30

Tyr Gln Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu
        35                  40                  45

Arg Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile
    50                  55                  60

Lys Glu Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Lys
65                  70                  75                  80

Gln Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu
                85                  90                  95

Met Gln Ser Thr Pro Pro Thr Asn Asn Arg Ala Arg Arg Glu Leu Pro
            100                 105                 110

Arg Phe Met Asn Tyr Thr Leu Asn Asn Ala Lys Lys Thr Asn Val Thr
        115                 120                 125

Leu Ser Lys Lys Arg Lys Arg Arg Phe Leu Gly Phe Leu Leu Gly Val
    130                 135                 140

Gly Ser Ala Ile Ala Ser Gly Val Ala Val Ser Lys Val Leu His Leu
145                 150                 155                 160

Glu Gly Glu Val Asn Lys Ile Lys Ser Ala Leu Leu Ser Thr Asn Lys
                165                 170                 175

Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr Ser Lys Val
            180                 185                 190

Leu Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu Pro Ile Val Asn
        195                 200                 205

Lys Gln Ser Cys Ser Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln
    210                 215                 220

Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu Phe Ser Val Asn
225                 230                 235                 240

Ala Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu Thr Asn Ser Glu
                245                 250                 255

Leu Leu Ser Leu Ile Asn Asp Met Pro Ile Thr Asn Asp Gln Lys Lys
            260                 265                 270

Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile
        275                 280                 285
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Met Ser Ile Ile Lys Glu Glu Val Leu Ala Tyr Val Val Gln Leu Pro
    290                 295                 300

Leu Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys Leu His Thr Ser Pro
305                 310                 315                 320

Leu Cys Thr Thr Asn Thr Lys Glu Gly Ser Asn Ile Cys Leu Thr Arg
                325                 330                 335

Thr Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe Phe
            340                 345                 350

Pro Gln Ala Glu Thr Cys Lys Val Gln Ser Asn Arg Val Phe Cys Asp
        355                 360                 365

Thr Met Asn Ser Leu Thr Leu Pro Ser Glu Ile Asn Leu Cys Asn Val
    370                 375                 380

Asp Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys Thr
385                 390                 395                 400

Asp Val Ser Ser Ser Val Ile Thr Ser Leu Gly Ala Ile Val Ser Cys
                405                 410                 415

Tyr Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile Ile
            420                 425                 430

Lys Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn Lys Gly Met Asp
        435                 440                 445

Thr Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn Lys Gln Glu Gly
    450                 455                 460

Lys Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile Asn Phe Tyr Asp Pro
465                 470                 475                 480

Leu Val Phe Pro Ser Asp Glu Phe Asp Ala Ser Ile Ser Gln Val Asn
                485                 490                 495

Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys Ser Asp Glu Leu
            500                 505                 510

Leu His Asn Val Asn Ala Gly Lys Ser Thr Thr Asn Ile Met Ile Thr
        515                 520                 525

Thr Ile Ile Ile Val Ile Ile Val Ile Leu Leu Ser Leu Ile Ala Val
    530                 535                 540

Gly Leu Leu Leu Tyr Cys Lys Ala Arg Ser Thr Pro Val Thr Leu Ser
545                 550                 555                 560

Lys Asp Gln Leu Ser Gly Ile Asn Asn Ile Ala Phe Ser Asn
                565                 570
```

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 15 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS:
- (D) TOPOLOGY: unknown

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/13694

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 39/395, 39/42; C12Q 1/00, 1/70; G01N 33/53
US CL : 424/130.1, 141.1, 147.1; 435/4, 5, 7.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/130.1, 141.1, 147.1; 435/4, 5, 7.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,81[illegible],524 A (BRAMS et al) 22 September 1998, cols. 12- 20.	1, 4, 10-15
Y		2, 3
X	US 5,824,307 A (JOHNSON) 20 October 1998, cols. 4-6.	1, 4, 10-15
Y		2, 3
X	US 5,880,104 A (LI et al) 09 March 1999, cols. 6-10.	1, 4, 10-15
Y		2, 3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 16 AUGUST 2000	Date of mailing of the international search report 05 SEP 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer BRETT NELSON Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/13694

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

WEST, DIALOG, MEDLINE
search terms: RSV, respiratory syncytial, monoclonal, antibodies, human, humanized, F protein, diagnostics, passive immunization, therapy, treatment